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THE BERIBERI HEART *

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One of the outstanding characteristics of many patients with beriberi is cardiac insufficiency. This type of cardiac insufficiency is caused by changes in the cardiovascular system which are dependent on a deficient diet. The deficiency has been shown to be due to a lack of vitamin B. In this paper, I wish to present the results of a study of two groups of patients with beriberi, directing special attention to the cardiovascular system. I shall emphasize and discuss certain differences that are present.

In the first group of fifteen patients, cardiac insufficiency was demonstrated, and in the second group of twelve patients no obvious symptoms of cardiac insufficiency were observed.

PATHOLOGIC CHANGES IN BERIBERI

The papers of Pekelharing and Winkler,[1] Nocht,[2] Muira,[3] Vedder,[4] Kasuma,[5] Herzog[6] and Scheube[7] may be consulted for a detailed description of the pathologic changes occurring in beriberi. For the purpose of this paper, the main pathologic changes may be grouped as follows: (1) degeneration of the peripheral nerves, including both the motor and the sensory elements; (2) edema of the subcutaneous tissues and muscles, and effusion of fluid into the serous cavities and (3) dilatation of the heart, particularly of the right side, with fatty infiltration and a moderate degeneration of the myocardium.

These changes lead to peripheral neuritis, edema of the tissues and signs of cardiac insufficiency. In many patients, one or the other group

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1. Pekelharing, C. A., and Winkler, C.: Mitteilungen über die Beriberi. Deutsche med. Wchnschr. **39**:845, 1887.

2. Nocht, B.: Beriberi Menses: Handbuch der Tropischen Krankheit, Leipzig, Johann Ambrosius Barth, 1924, vol. 2, p. 450.

3. Muira, K.: Beriberi oder Kakke, Ergebn. d. inn. Med. u. Kinderh. **4**:280, 1909.

4. Vedder, E. B.: Beriberi, New York, William Wood & Company, 1913.

5. Kasuma: Ueber die veränderungen des Herzens und Gefäss System bei Kakke (Beriberi), Third Congress, Saigon, 1913, Far Eastern A. Trop. Med. **3**: 383, 1914.

6. Herzog, M.: Studies in Beriberi, Philippine J. Sc. **1**:709, 1906.

7. Scheube: Die Beriberi Krankheit., Jena, Gustav Fischer, 1894.

of symptoms predominates, and in order to emphasize this fact the following classification has been used by many: (1) neuritic type, (2) edematous type, (3) mixed type and (4) cardiac type.

PATIENTS WITH CARDIAC INSUFFICIENCY

In this group there were fifteen patients. Their main complaints were typical of those suffering from cardiac insufficiency. Thirteen survived and two died. One of the patients who died had extensive pulmonary tuberculosis; the other had diaphragmatic and intercostal paralysis with bronchopneumonia. Both of these patients had cardiac enlargement, tachycardia and signs of congestive heart failure.

Symptoms and Signs of Cardiac Insufficiency.—All the patients complained of excessive fatigue and palpitation on exertion. Shortness of breath was felt, but it was not so pronounced as the first two symptoms. Edema of the lower extremities was present in every case, and in many it was the first sign of the disease. One must be cautious in attributing edema to a failing heart under such conditions, since it is frequently a symptom without any other supporting evidence of heart failure. In these patients, the edema was never considered to be the result of cardiac insufficiency unless there were other unequivocal signs. Four of the patients had enlarged livers. Ascites was present in one, and hydrothorax could be demonstrated in four. There were signs of pulmonary congestion in only three patients.

Examination of the heart revealed a cardiac rate that varied from 52 to 136 beats per minute, the average being 106. The rhythm was normal. The heart rate was labile, the slightest exertion causing a great increase. There was engorgement of the cervical veins with increased pulsation in four patients. Increased arterial pulsation with a collapsing pulse, capillary pulsation and increased arterial sounds over the brachial and femoral vessels were present in five patients.

The cardiac impulse was usually feeble and diffuse. A systolic thrill was felt over the apex in four patients, and in two patients a palpable thrill could be felt over the carotid vessels in the neck.

The cardiac dulness was increased in every case. The increase occurred both to the right and to the left of the midsternal line, and in the second and third left intercostal spaces. Associated with the cardiac enlargement there were systolic murmurs at the apex and over the pulmonary area in ten cases. The pulmonary second sound was accentuated in ten of the patients. There were no diastolic murmurs.

Neurologic Symptoms and Signs.—The changes in the nervous system were comparatively mild. The most severe changes were noted in the two patients who died. In one of these there was a motor and sensory paralysis of both legs, and in the other there was diaphragmatic

and intercostal paralysis. In all the other patients, the neuritis was mild and varied in degree. The knee and ankle jerks were absent, but the muscular power was good, except in the two patients who died.

The sensory disturbances were mild, and when they occurred they consisted of a diminution of touch and vibratory sense. The sensation of touch was diminished over a greater area than were the other sensations, and this feature was much more marked in the presence of edema.

The striking feature in these cases was the comparative lack of extensive neurologic changes, and the preservation of muscular power. This is of considerable importance, since the patients who have the most marked changes in the central nervous system, have the least changes in the cardiovascular system. This point will later be discussed in greater detail.

Blood Pressure.—There were no constant changes in the blood pressure. It was either normal, increased or decreased. The systolic pressure varied from 82 to 150 and the diastolic from 35 to 100 millimeters of mercury. The pulse pressure averaged 45. If the blood pressure was high during the acute stage of the illness, it gradually became normal during convalescence. The systolic pressure usually fell before the diastolic pressure became normal. In some, the systolic pressure fell as the diastolic increased, and in others, both pressures increased simultaneously. Although an increased pulse pressure was not a constant feature in these cases, it was not an uncommon observation. It was obvious, however, that the patients with the highest pulse pressures were the ones with the most marked peripheral vascular changes. There was no correlation between the size of the heart and the changes in the blood pressure.

These observations are in agreement with those of previous investigators, such as Aalsmeer and Wenkebach,[8] Muira [3] and Shimazono.[9] If the changes in blood pressure play a rôle in the cardiac enlargement, they are merely contributory, not primary.

Electrocardiographic Examination.—The results of the electrocardiographic examinations are summarized briefly in table 1. It is remarkable that there were no characteristic changes from the normal. The rate was usually increased. The mechanism was normal in every case, and arryhthmias were not observed, except in one patient who had extrasystoles and sinus bradycardia during convalescence. Right ventricular preponderance was present in two patients.

The height of the ventricular complexes was low in four patients. In these patients, the voltage became higher during convalescence. In

8. Aalsmeer, W. C., and Wenkebach, K. F.: Herz und Kreislauf bei der Beriberi Krankheit, Wien. Arch. f. inn. Med. **16**:193 (Jan.) 1929.

9. Shimazono: Stepp. Die avitaminosen, Berlin, Julius Springer, 1927.

others, the waves which were high during the acute stage of the disease became lower as they improved.

The P-R interval varied from 0.13 to 0.20 second, the average being 0.16 second. In three patients, the P-R interval decreased during convalescence and in one patient it increased.

TABLE 1.—*Electrocardiograms of Patients with Beriberi and Signs of Cardiac Insufficiency*

No.	Rate per Minute	Rhythm	P-R Interval, Seconds	Diagnosis	Remarks
1	107	Sino-auricular	0.20	Normal mechanism; sinus tachycardia; right ventricular preponderance	T_2 iso-electric; T_3 negative
2	52	Sino-auricular	0.16	Normal mechanism	P_3 negative; T_3 negative; R_3 notched
3	100	Sino-auricular	0.16	Normal mechanism	Low voltage in lead 3
3a	85	Sino-auricular	0.16	Normal mechanism	R_3 notched
4	96	Sino-auricular	0.16	Normal mechanism	
5	120	Sino-auricular	0.17	Normal mechanism	R wave notched in all leads
5a	110	Sino-auricular	0.14	Normal mechanism	
6	136	Sino-auricular	0.16	Sinus tachycardia	Died; diaphragmatic paralysis
7	88	Sino-auricular	0.16	Normal mechanism; right ventricular preponderance	
8	134	Sino-auricular	0.20	Normal mechanism	
8a	105	Sino-auricular	0.14	Normal mechanism	
9	100	Sino-auricular	0.16	Normal mechanism	Low voltage in lead 1; T_2 high
9a	88	Sino-auricular	0.16	Normal mechanism	Low voltage in leads 1 and 3; P_3 flat and T_3 negative
10	118	Sino-auricular	0.16	Normal mechanism	
11	130	Sino-auricular	0.16	Normal mechanism	Died; pulmonary tuberculosis
12	120	Sino-auricular	0.16	Normal mechanism	T_3 positive
12a	120	.....	0.16	Normal mechanism	T_3 negative
b	65	.....	0.16	Normal mechanism	T_3 negative
c	48	.....	0.12	Normal mechanism	T_3 positive
d	48	.....	0.12	Normal mechanism	T_3 positive
13	80	Sino-auricular	0.16	Normal mechanism	
	45	Sino-auricular	0.18	Normal mechanism	Ventricular extrasystole
14	115	Sino-auricular	0.13	Normal mechanism	
15	100	Sino-auricular	0.16	Normal mechanism	T_2 high
15a	88	Sino-auricular	0.16	Normal mechanism	Low voltage in leads 1 to 3; P_3 flat; T_3 negative

In five cases, the T waves were negative in lead 3. In one of these, T_3 became positive during the convalescence of the patient, and in two it became negative. These changes occurred without the use of digitalis. In some cases during the acute stage, the T waves in lead 2 were high, and became lower during recovery.

Aalsmeer and Wenkebach [8] pointed out that the electrocardiograms of patients with beriberi are normal. They did not observe abnormal rhythms or changes in conduction. There was a tendency for some to show right ventricular preponderance, and the height of the ventricular waves was at least normal or sometimes increased. In some of their

cases, the P-R interval was shortened during the acute stage, and became longer during convalescence. I have observed this phenomenon only twice.

Scott and Hermann [10] stated, from the study of their cases, that there were no characteristic or pathognomonic electrocardiographic changes. Although they recognized that the complexes might be small, this was attributed to the presence of subcutaneous edema. They also described negative T waves in leads 1 and 3, and some patients showed a slight to moderate left ventricular preponderance, and some slurring and slight aberration in the ventricular complexes. They were of the opinion that the changes observed were evidences of definite myocardial changes, even in mild cases.

In the case of beriberi reported by Kepler,[11] the electrocardiogram was normal.

In summary, then, it may be stated that in the division of patients with cardiac insufficiency there were no characteristic changes in the electrocardiograms, but there was some evidence of myocardial changes in a few.

Roentgen Examination of the Heart.—One of the best methods of studying the changes that occur in the size and configuration of the heart in beriberi is by means of teleoroentgenograms. The results of such a study in a few cases with heart failure are recorded in table 2. The changes in size and configuration can also be seen in charts 1, 2, 3 and 4.

Previous roentgenologic observations of the heart in patients with beriberi were made by Muira,[3] Reinhard,[12] Aalsmeer and Wenkebach [8] and Ido and Watanabe.[13] Each of these authors called attention to the fact that in many of the patients there is considerable enlargement of the right side of the heart.

In the present study, the diaphragm was examined for mobility, and its level determined on the two sides. The transverse diameter and the width of the shadow cast by the large vessels at the base of the heart were measured. Then, the surface area of the heart was measured

10. Scott, L. C., and Hermann, G. R.: Beriberi (Maladie des Jambes) in Louisiana with Especial Reference to Cardiac Manifestations, J. A. M. A. **90**: 2083 (June 30) 1928.

11. Kepler, E. S.: Beriberi from a Diet of Raw Starch, J. A. M. A. **85**:409 (Aug. 8) 1925.

12. Reinhard, P.: Roentgenbefunde bei beriberiartigen Erkrankungen, Arch. f. Schiffs- u. Tropen-Hyg. **20**:51, 1916; Roentgenbefunde bei Beriberi, Fortschr. a. d. Geb. d. Röntgenstrahlen **24**:104, 1916.

13. Ido and Watanabe: The Orthodiagraphic Examination of the Heart in Beriberi, Sei-i-kwai M. J., Tokyo **33**:35, 1914.

TABLE 2.—*Roentgen Examination of the Heart in Patients with Beriberi and Signs of Cardiac Insufficiency*

Patient	Day of Observation	Diaphragm: Motility (Fluoroscopic Examination)	Diaphragm: Position, Right	Diaphragm: Position, Left	Transverse Diameter, Cm.: To Right of Midsternal Line	Transverse Diameter, Cm.: To Left of Midsternal Line	Transverse Diameter, Cm.: Total	Surface Area of Heart: Estimated Normal, Sq. Cm.	Surface Area of Heart: Measured Area, Sq. Cm.	Surface Area of Heart: Oversize, Sq. Cm.	Surface Area of Heart: Aorta, Cm.	Remarks
1	1st day	Movement normal	10th rib	10th rib	5.6	10.7	16.3	107.56	157.3	49.74	6.4	Pleural effusion
	8th day	Movement normal	10th rib	10th rib	4.4	9.3	13.7	104.07	131.9	27.83	5.9	
	16th day	Movement normal	11th rib	11th rib	3.7	8.9	12.6	104.01	124.8	27.90	5.6	
2	1st day	Movement normal	10th rib	.....	3.4	12.3	15.7	98.11	132.0	44.10	5.5	
	14th day	Movement normal	10th rib	10th rib	3.9	10.0	13.9	96.00	118.5	22.50	4.0	
	24th day	Movement normal	10th rib	10th rib	3.3	9.6	12.9	96.00	118.2	21.00	4.8	
3	1st day	Movement normal	9th rib	.....	4.9	10.5	15.4	98.56	124.0	25.44	6.0	
	7th day	Movement normal	9th rib	10th rib	4.0	8.8	12.8	96.00	106.5	10.00	4.8	
	24th day	Movement normal	10th rib	10th rib	3.2	8.9	12.1	96.00	106.5	10.00	4.8	
4	1st day	Movement normal	10th rib	.....	4.0	10.1	14.1	104.01	126.2	22.00	4.8	
	15th day	Movement normal	10th rib	11th rib	4.1	8.3	12.4	104.01	106.5	2.00	5.0	
5	1st day	.....	.....	8th rib	3.8	8.4	12.2	.....	.....	... .	...	Pleural effusion
	27th day	.....	9th rib	10th rib	3.0	7.5	10.5					
6	1st day	Movement normal	9th rib	10th rib	5.2	10.2	15.4	95.10	146.5	51.00	5.5	
7	1st day	.....	9th rib	.....	5.5	....	....	.....	.....	.....	...	Bilateral effusion
	14th day	.....	9th rib	10th rib	6.4	7.7	14.1	92.00	99.0	7.00	5.0	Pleural effusion on the left side
8	1st day	Movement normal	.....	8th rib	3.8	8.0	11.8	.....	.....	.....	...	Pleural effusion

according to the method described by Hodges and Eyster,[14] and the variation from normal calculated in square centimeters.

There was an enlargement of the heart in all cases. It was due principally to an increase in the size of the right auricle and right ventricle. The right ventricle was enlarged outward and upward, and the right auricle was increased outward.

Another striking feature was an increase in the shadow in the region of the pulmonary artery. This was undoubtedly due to an increase in the size of the conus arteriosus and the pulmonary artery.

Besides these changes, the shadow of the vessels at the base of the heart was often increased, particularly to the right. This was due to an increase in the shadow cast by the superior vena cava. It can be readily seen in the x-ray picture taken in case 4.

The left auricle and the left ventricle shared to a less extent in the cardiac enlargement, since examination of the heart in the left and right anterior oblique positions revealed only moderate enlargement of these structures.

The size and configuration of the heart was followed by repeated roentgen examinations during the course of the illness, and interesting changes were observed. The heart decreased in size in a short time, and the configuration became that of a normal heart. The shadow of the vessels at the base also decreased, and the pulmonary artery became less prominent.

In summary, it may be stated that roentgen examination of the heart recorded a change in the size and configuration of the heart in these patients. The enlargement was due to an increase in the right auricle and the right ventricle, the pulmonary artery and the superior vena cava. A decrease in the size of the heart occurred rapidly following proper therapy.

The cases herein reported illustrate the various changes that may occur.

REPORT OF CASES

CASE 1.—*History.*—A Chinaman, aged 18, was first seen in the outpatient department of the Peiping Union Medical College one month before admission to the hospital. He complained of swelling of the legs and face. His previous history was unessential.

He had always enjoyed excellent health until one week before coming under observation. At that time, he began to notice excessive fatigue on exertion, and edema of the lower extremities. He had palpitation after walking, but little shortness of breath; otherwise he felt well.

14. Hodges, P. C., and Eyster, J. A. E.: Estimation of Cardiac Area in Man, Am. J. Roentgenol. **12**:252 (Sept.) 1924.

Examination.—On examination, he was found to be well nourished and well developed, and did not appear acutely ill. There was no fever. The mucous membranes were normal. There was moderate edema of the face, legs and thighs. The lungs were clear. The heart was enlarged. The cardiac dulness extended 10.5 cm. to the left of the midsternal line in the fifth intercostal space, and 5.5 cm. to the right in the fourth intercostal space. There were no shocks or thrills; the point of maximum impulse was diffuse and rather feeble. There was a systolic murmur at the apex and over the pulmonic area, and the pulmonary second sound was accentuated. There were no diastolic murmurs. The blood pressure was 116 millimeters of mercury systolic, and 46 diastolic. The pulse was collapsing in type, and one could observe distinct capillary pulsation in the nail beds. The liver was not enlarged and there was no ascites. The knee and ankle jerks were not obtained. The Wassermann reaction of the blood was negative. The urine showed a small amount of albumin but no casts.

The patient refused to enter the hospital, but returned to the outpatient clinic at different intervals for twenty-seven days. During this time, in spite of a limitation of his activities and the administration of digitalis, he became progressively worse. The edema increased, the pulse pressure became higher, the heart rate became more rapid and the liver became enlarged.

Later, on admission to the hospital, he appeared comfortable at rest, although a generalized anasarca was present. There was neither orthopnea nor cyanosis. There was moderate engorgement of the cervical veins, and accentuated pulsation of the peripheral vessels. There was evidence of a pleural effusion on the right side, and a moderate amount of free fluid in the peritoneal cavity. The pulse, collapsing in type, was increased in rate, and the rhythm was regular. There was distinct capillary pulsation, and the arterial sounds over the large vessels were rather loud.

Examination of the heart at this time revealed the apex impulse to be in the fifth intercostal space 13 cm. to the left of the midsternal line. It was diffuse and forceful. By percussion, the heart was found to be enlarged to the left and right of the midsternal line; the transverse diameter measured 16 cm. There were loud systolic murmurs at the apex and over the pulmonic areas, and the pulmonary second sound was accentuated. The blood pressure was 150 millimeters of mercury systolic and 60 diastolic. The lungs did not show any signs of pulmonary congestion. The liver was enlarged. The knee and ankle jerks were absent. There was mild hypesthesia to touch, pain and vibration over the legs. The muscular power was good, except in the anterior tibial muscles, where there was a slight weakness.

There was no anemia. The urine was normal and the phenolsulphonphthalein test showed an excretion of 55 per cent in two hours. There was a normal gastric acidity after the administration of beta-iminazolyl-ethylamine hydrochloride. The basal metabolic rate was —8.4 per cent and the nonprotein nitrogen of the blood was 35.4 mg. per hundred cubic centimeters.

The course of illness can be followed by means of chart 1. It may be seen that as long as the patient remained ambulatory, the cardiac rate was high, the edema increased, the systolic blood pressure and the pulse pressure both increased, the size of the heart increased and the symptoms of the patient became worse. There were definite changes in the electrocardiographic tracings, and digitalis caused no improvement. With rest in bed and an adequate diet, supplemented by 3 Gm. of yeast daily, a most remarkable change in the clinical picture was produced. The cardiac rate decreased, the systolic blood pressure fell, the diastolic pressure rose, and there was a marked diuresis with a corresponding loss in weight. The heart decreased markedly in size. The electrocardiographic trac-

ings changed, and the patient became symptomatically well. With the decrease in the size of the heart and with the changes in the blood pressure, the murmurs, the peripheral pulsation, the capillary pulse and the pistol shot sounds disappeared. The knee jerks did not return while the patient was under observation.

Summary.—A young man showed a gradual development of edema of the extremities and face, with signs of cardiac enlargement, valvular insufficiency and tachycardia, changes in the blood pressure, peripheral pulsation, capillary pulsation, pistol shot sounds over the large vessels, and signs of congestive heart failure which were predominantly of the right side. He failed to improve on a restriction of his activities and the administration of digitalis, but with rest in bed and an antiberiberi diet supplemented by 3 Gm. of yeast daily, all the signs of cardiac insufficiency disappeared. The disturbances of the nervous system were mild and persisted longer than the cardiac symptoms.

CASE 2.—*History.*—A Chinaman, aged 19, complained of weakness, numbness and swelling of the lower extremities. His previous health had been good until three months before he came under observation. At that time, he began to notice some edema of the ankles and numbness of the legs. Three weeks before admission, the edema increased, and he began to have dyspnea, on moderate exertion, and palpitation of the heart.

Examination.—On examination, he appeared comfortable at rest, and there was no dyspnea, orthopnea or cyanosis. There was moderate edema of the face with engorgement of the veins of the neck, and the pulsation in the vessels of the neck was forceful. The heart was enlarged. The cardiac dulness extended 12 cm. to the left of the midsternal line in the fifth intercostal space, and 3 cm. to the right in the fourth intercostal space. There was a loud systolic murmur at the apex and over the pulmonary area, and the pulmonary second sound was accentuated. The blood pressure was elevated—150 millimeters of mercury systolic and 100 diastolic. The lungs were clear. There was a slight enlargement of the liver. There was edema of the legs, with some tenderness of the calf muscles and a loss of the knee and ankle jerks. There was slight hypesthesia to touch and pain over the legs. It was especially noteworthy that the gait and muscular power were normal.

There was no anemia, the urine was normal and the excretion of phenolsulphonphthalein was 70 per cent in two hours. The electrocardiogram showed a normal mechanism, with negative P and T waves in lead 3. The Wassermann reaction was negative.

The course of the patient's illness can be followed by means of chart 2. It is evident that the cardiac rate decreased, the body weight diminished, the edema disappeared, the blood pressure became lower, the heart decreased in size, and there was a corresponding improvement in the patient's symptoms. The murmurs over the heart disappeared and the patient became symptomically well, although the deep reflexes did not return while he was under observation. All these changes occurred with rest in bed and an antiberiberi diet supplemented by 3 Gm. of yeast daily.

Summary.—A youth who had lived on a diet of rice with a few green vegetables showed an increasing edema, mild neuritis and cardiac insufficiency. On examination, he had signs of a heart failure on the right side, cardiac enlargement and valvular insufficiency, all of which disappeared after dietary treatment. One of the important features of the illness was the presence of cardiac insufficiency with mild neurologic disturbances.

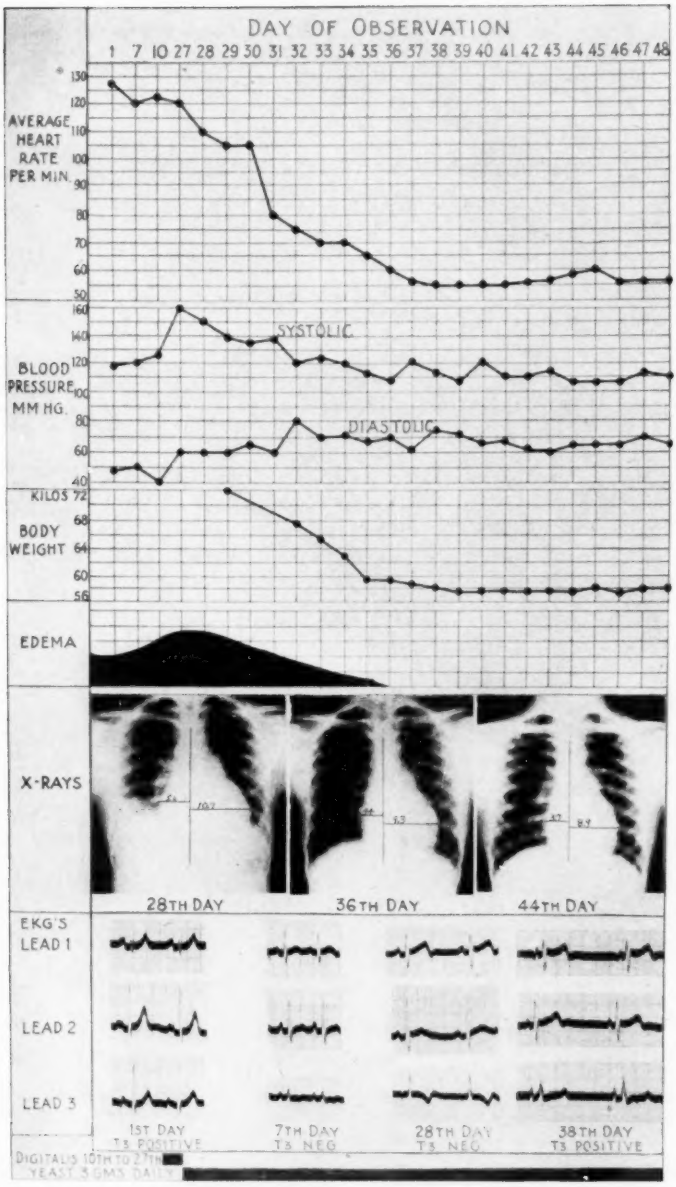

Chart 1 (case 1).—Results of examinations made during the upward course of the illness, and on treatment with rest in bed and an antiberiberi diet.

CASE 3.—*History.*—A Chinaman, aged 19, was admitted to the hospital complaining of a swelling of the legs and ankles that had endured for three weeks, and moderate shortness of breath after exertion that had endured for one week. For about eight months he had been living on a diet consisting chiefly of boiled rice and vegetables. His symptoms had begun insidiously without any signs of cardiac insufficiency. He first had noticed swelling of the legs. Following the

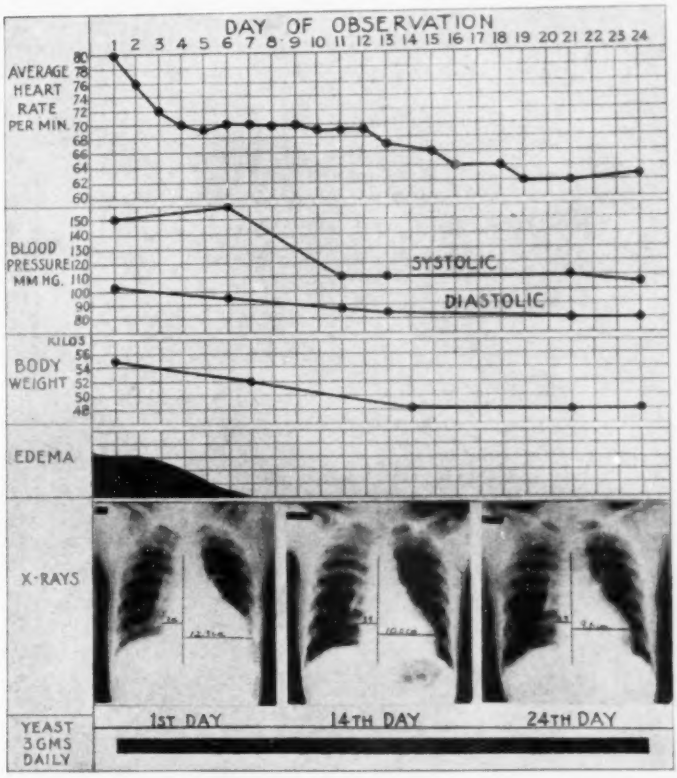
DAY OF OBSERVATION
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
AVERAGE HEART RATE PER MIN.
80 78 76 74 72 70 68 66 64 62 60
BLOOD PRESSURE MM HG.
150 140 130 120 110 100 90 80
SYSTOLIC
DIASTOLIC
KILOS
BODY WEIGHT
56 54 52 50 48
EDEMA
X-RAYS
1ST DAY
14TH DAY
24TH DAY
YEAST 3 GMS DAILY

Chart 2 (case 2).—Improvement in beriberi with cardiac insufficiency when patient was at rest in bed and on antiberiberi diet.

appearance of the edema, he had begun to have shortness of breath and palpitation on exertion.

Examination.—On examination, he appeared comfortable at rest. There was no dyspnea, orthopnea or cyanosis. There was engorgement of the cervical veins with slight puffiness of the face. The lungs were clear. The heart was enlarged. There was a systolic murmur at the pulmonic area. The sounds at the apex were clear. The blood pressure and the pulse were normal. The liver was enlarged,

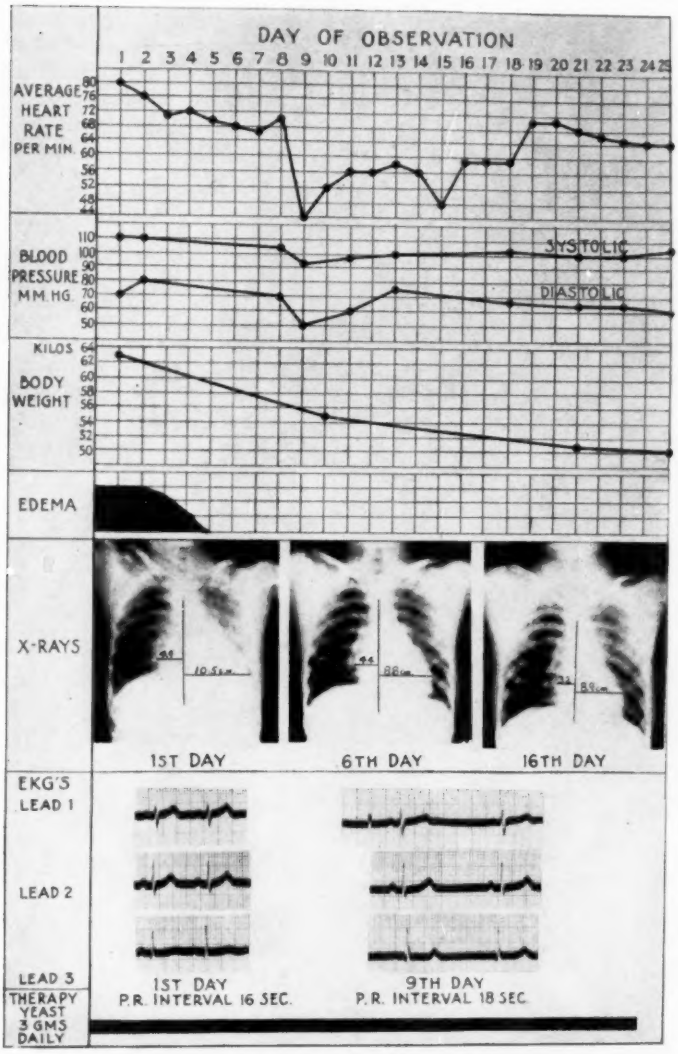

Chart 3 (case 3).—Effect of rest in bed and an antiberiberi diet on patient with beriberi and cardiac insufficiency.

and there was edema of the legs. The knee and ankle jerks were absent. There were no sensory disturbances and the muscular power, it is to be noted, was normal.

The Wassermann reaction was negative. There was no anemia. The urine was clear. The excretion of phenolsulphonphthalein was 55 per cent in two hours. The x-ray pictures and electrocardiograms are shown in chart 3.

Chart 3 illustrates the course of the illness. It may be seen that the rate was never excessively rapid, but with improvement it became slow. The blood pressure decreased, the weight diminished and the edema disappeared within five days. The heart likewise decreased in size, and the electrocardiogram changed. The knee jerks did not reappear while the patient was under observation.

Summary.—A young man showed a development of the symptoms and signs of cardiac insufficiency with mild neurologic disturbances. All the signs of heart failure subsided rapidly following an adequate diet supplemented with yeast.

SUMMARY OF OBSERVATIONS IN CASES OF BERIBERI WITH CARDIAC INSUFFICIENCY

In regard to the clinical features of the patients who had cardiac insufficiency, it may be said that most of them complained of palpitation, edema and some shortness of breath on exertion. These symptoms sometimes were preceded by pains in the calf muscles. If the patient was seen early in the course of his illness, it was noted that the heart rate was somewhat accelerated. The blood pressure might be normal. There were no conspicuous changes in the peripheral vessels. The heart was enlarged both to the right and to the left of the midsternal line; the apex beat was diffuse, and not forceful. There was usually a systolic murmur over the pulmonary area, and the pulmonary second sound was accentuated. The lungs did not show signs of congestion, and the liver was not enlarged. There was usually edema of the lower extremities.

As the disease progressed, all these signs became exaggerated and the edema increased. The liver became enlarged, and nausea and vomiting sometimes appeared. Striking changes occurred in the peripheral circulation. There might be increased peripheral pulsation of the vessels of the neck and extremities, with a collapsing type of pulse and capillary pulsation. The sounds over the brachial and femoral arteries were increased. Examination of the heart revealed an increased enlargement with a systolic apical thrill, and loud systolic murmurs over the mitral and pulmonary areas. The rhythm, however, remained regular and it seemed clear that the common arrhythmias do not occur in this disease. Teleoroentgenograms of the heart revealed enlargement of the right auricle and the right ventricle, with a prominent pulmonary artery and a prominent superior vena cava. The electrocardiograms did not show anything characteristic. The voltage might be low or high. Minor abnormalities, such as changes in the T waves, might be present.

All these conditions might occur in the cardiovascular system with slight changes in the nervous system. The latter generally consisted of minor sensory disturbances and a loss of the knee and ankle jerks.

When the patient was treated with rest in bed and an antiberiberi diet supplemented with yeast, striking changes occurred. The heart rate fell, the blood pressure became normal, the peripheral pulsation and the collapsing and capillary pulse disappeared, diuresis set in, the heart became smaller, the murmurs disappeared and the patient became normal. The deep reflexes did not reappear until many weeks after the cardiac signs disappeared.

PATIENTS WITHOUT CARDIAC INSUFFICIENCY

In contrast to the patients with cardiac insufficiency, those without cardiac insufficiency complained chiefly of symptoms referable to the nervous system. However, it was of considerable interest to study the cardiovascular system of these patients, in order to determine whether or not there was evidence of any disturbance in spite of the lack of symptoms referable to the heart.

Cardiac Signs.—The heart rate was found to be lower than in the former group, the average being 75 beats per minute. The heart was enlarged in three patients. In one of these, the blood pressure was low, and there was a systolic murmur over the mitral and pulmonary areas. In the others, the heart was of normal size and there were neither murmurs nor any other signs of changes in the cardiovascular system.

The blood pressure was practically the same in this group as in the former; namely, in some it was normal, in others either elevated or below normal.

Electrocardiographic Examination.—The electrocardiograms were essentially the same as those of the group with cardiac insufficiency. The observations are summarized briefly in table 3. The rhythm was always regular. Right ventricular preponderance was present in three patients, and left ventricular preponderance in two. The voltage was low in five and the P-R interval was lengthened to 0.2 second in two. The T wave was negative in leads 1 and 2 in one case and negative in lead 3 in two. The T wave was also high in lead 2 in three cases.

It may be seen, therefore, that in spite of the absence of symptoms of cardiac insufficiency minor electrocardiographic changes were present, indicating that the myocardium was involved before symptoms of insufficiency appeared.

Roentgen Examination of Heart.—The results of the roentgen examinations in this group of patients are recorded in table 4. Two of the patients showed definite cardiac enlargement. The type of enlargement was the same as that in the former group.

Neurologic Examination.—In the discussion of the patients with heart failure, it was stated that the neurologic disturbances were

TABLE 3.—*Electrocardiograms of Patients with Beriberi Without Signs of Cardiac Insufficiency*

No.	Heart Rate per Minute	Rhythm	P-R Interval, Seconds	Diagnosis	Remarks
1	100	Sino-auricular	0.16	Normal mechanism	
2	75	Sino-auricular	0.16	Normal mechanism; right ventricular preponderance	Low voltage in lead 1
3	55	Sino-auricular	0.16	Normal mechanism	Low voltage in all leads; T_2 and T_3 negative
	60	Sino-auricular	0.16	Normal mechanism	Negative
4	110	Sino-auricular	0.14	Normal mechanism; left ventricular preponderance	P wave and T wave negative in lead 3
5	50	Sino-auricular	0.14	Sinus bradycardia	
6	84	Sino-auricular	0.18	Normal mechanism	Low voltage in lead 1; high T_2
7	80	Sino-auricular	0.16	Normal mechanism; left ventricular preponderance	T_3 negative
8	76	Sino-auricular	0.16	Normal mechanism	Low voltage in lead 1
9	90	Sino-auricular	0.16	Normal mechanism; right ventricular preponderance	Low voltage in all leads
10	65	Sino-auricular	0.20	Normal mechanism; sinus arrhythmia	T_2 high
11	86	Sino-auricular	0.15	Normal mechanism	T_1 negative
	99	Sino-auricular	0.15	Normal mechanism	T_1 iso-electric
	96	Sino-auricular	0.14	Normal mechanism	T_1 positive; T_2-T_3 high
12	65	Sino-auricular	0.20	Normal mechanism	T_3 negative
12a	60	Sino-auricular	0.18	Normal mechanism	T_3 high

TABLE 4.—*Results of the Roentgen Examination of the Heart in Patients with Beriberi Without Signs of Cardiac Insufficiency*

Patient	Day of Observation	Diaphragm: Motility (Fluoroscopic Examination)	Diaphragm: Position: Right	Diaphragm: Position: Left	Transverse Diameter, Cm.: To Right of Midsternal Line	Transverse Diameter, Cm.: To Left of Midsternal Line	Transverse Diameter, Cm.: Total	Surface Area of Heart: Estimated Normal, Sq. Cm.	Surface Area of Heart: Measured Areas, Sq. Cm.	Surface Area of Heart: Oversize, Sq. Cm.	Aorta, Cm.
1	1st	Movement normal	10th rib	11th rib	5.5	9.7	15.2	103.48	148.0	45.4	6.6
	5th	Movement normal	10th rib	11th rib	4.8	8.9	13.7	103.48	121.3	17.8	6.4
	15th	Movement normal	10th rib	11th rib	4.2	7.6	11.8	102.80	92.9	10.0	6.5
2	1st	Movement normal	10th rib	10th rib	5.0	9.5	14.5	96.18	134.5	38.0	4.7
3	1st	Movement normal	10th rib	11th rib	4.3	8.7	13.0	102.61	107.9	5.3	4.7
4	1st	Movement normal	10th rib	10th rib	3.3	8.1	11.4	94.33	89.0	5.0 (under size)	4.3
5	1st	Movement normal	10th rib	11th rib	5.0	7.8	12.8	.....	.....	....	5.2
6	1st	Movement normal	10th rib	9th rib	3.2	8.6	11.8				
7	1st	Movement normal	10th rib	11th rib	4.0	7.0	11.0				
	11th	Movement normal	10th rib	10th rib	3.5	7.0	10.5				
8	1st	Movement normal	10th rib	10th rib	3.0	8.1	11.1				

comparatively mild except in the two fatal cases. In this group, the neurologic disturbances predominated. The observations have been tabulated in table 5. It may be readily observed that in the patients without heart failure, both the motor and the sensory disturbances were marked. None of them had normal muscular power in the legs, five had diminished muscular power and seven were completely paralyzed. The three patients with enlarged hearts had only diminished muscular power, and were still able to walk with some assistance.

None of the others had cardiac enlargement. On the other hand, in the group with heart failure, ten patients had normal muscular power in the legs, four had diminished muscular power and only one had complete loss of muscular power. The sensory changes were mild.

The case to be reported illustrates the changes that may occur without heart failure.

TABLE 5.—*Neurologic Disturbances in Patients with Beriberi*

						Sensory Conditions				
Groups Studied	Total Number of Cases	Loss of Knee Kicks and Ankle Jerks	Normal Muscular Power	Diminished Muscular Power	Paralysis of Legs	Normal	Sense of Touch Absent	Sense of Vibration Absent	Sense of Pain Absent	Sense of Temperature Absent
Patients with heart failure	15	15	10	4	1	12	3	1	0	0
Patients without heart failure	12	12	0	5	7	2	10	6	5	5

REPORT OF CASE

CASE 4.—*History.*—A Chinaman, aged 27, entered the hospital complaining of a slight edema of the extremities, of four months' duration, and weakness of the legs, of six weeks' duration. For the past four years, he had lived on a diet that consisted principally of rice and wheat. He seldom ate meat and on rare occasions had vegetables with his meals.

For several months he had noticed swelling of his legs, and slight puffiness about the eyes in the morning. For one month before admission he had noticed progressive weakness of both legs, and this had increased until he was able to stand or walk only when assisted. He had also had some numbness and tingling of the lower extremities, and some pain in his legs, especially on pressure. He had never had shortness of breath or palpitation. It is important to note that his disability was due to weakness of the legs and inability to walk.

Examination.—On examination, he appeared comfortable at rest. He could stand on his feet only with assistance. There were no signs of congestive heart failure, and no dyspnea, orthopnea or cyanosis. The cervical veins were not engorged, and the lungs were normal. The apex beat of the heart was 11 cm. from the midsternal line, and the impulse was diffuse. There were no thrills. The heart was enlarged. The cardiac dulness extended 11 cm. to the left of the midsternal line in the fifth intercostal space, and 4 cm. to the right of the midsternal line in the fourth intercostal space. The rate was 90 per minute and the rhythm regular. At the apex there was a soft systolic murmur, and over the

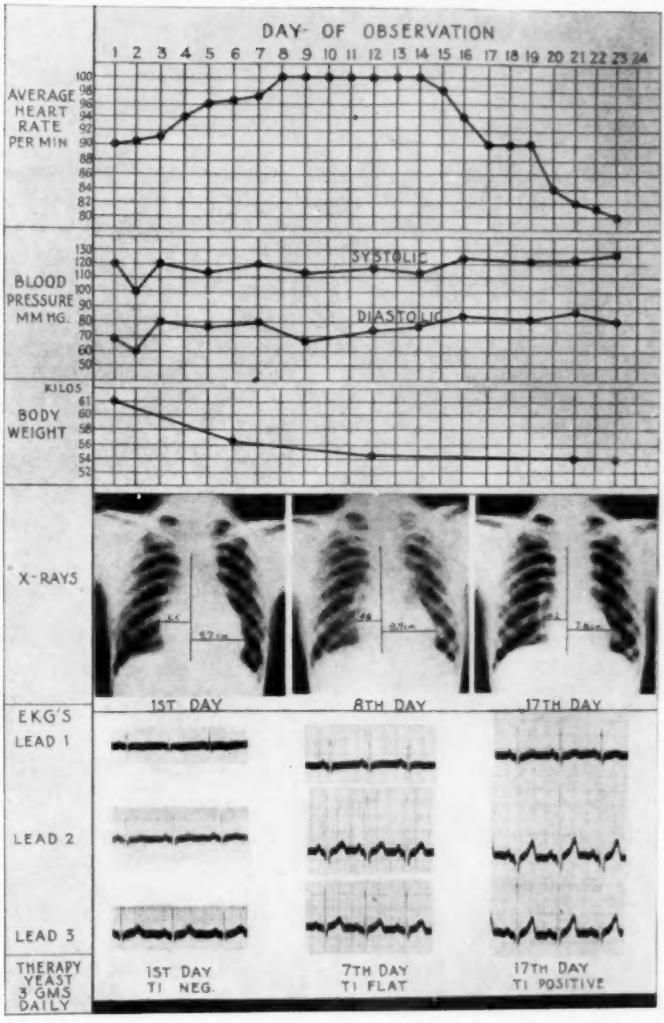
DAY OF OBSERVATION
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
AVERAGE HEART RATE PER MIN
100 98 96 94 92 90 88 86 84 82 80
BLOOD PRESSURE MM HG.
130 120 110 100 90 80 70 60 50
SYSTOLIC
DIASTOLIC
KILOS
BODY WEIGHT
61 60 58 56 54 52
X-RAYS
1ST DAY
8TH DAY
17TH DAY
EKG'S
LEAD 1
LEAD 2
LEAD 3
THERAPY YEAST 3 GMS DAILY
1ST DAY T1 NEG.
7TH DAY T1 FLAT
17TH DAY T1 POSITIVE

Chart 4 (case 4).—Observations in a case of beriberi without cardiac insufficiency. The treatment consisted of rest in bed and an adequate diet.

pulmonary area a loud systolic murmur followed by a loud accentuated second sound. The blood pressure was normal, and there was no capillary pulsation or increased sounds over the peripheral arteries.

Examination of the nervous system revealed marked diminution of the muscular power in the legs, particularly in the anterior tibial muscles. There was no atrophy. The deep reflexes were absent. Plantar response was normal. There was hypesthesia to touch from the middle of the thigh downward. The sense of vibration was lost over the legs, and there was a diminution of the pain sense.

There was no anemia. The urine was clear and the excretion of phenolsulphonphthalein was 45 per cent in two hours. The Wassermann reaction was positive. The ocular fundi were normal. The results of the electrocardiographic and roentgen examinations are recorded in chart 4.

The patient's clinical course can be followed from chart 4. With rest in bed and 3 Gm. of yeast daily, the heart decreased in size, the heart rate gradually fell and the patient's general condition improved. He regained some of his muscular power and was able to walk, but the deep reflexes did not return while he was under observation.

Summary.—A man with signs of an extensive polyneuritis and inability to walk, had cardiac enlargement without symptoms or signs of cardiac insufficiency. This illustrates the fact that the heart may be involved in patients with beriberi, even though they do not have symptoms or signs of heart failure.

The only way in which this patient differed from those with heart failure was in the absence of signs of congestive heart failure and the presence of signs of an extensive polyneuritis. The same type of cardiac enlargement and electrocardiographic changes were present, but other signs failed. It is highly probable that myocardial failure would have appeared if the patient had been capable of carrying on normal activities.

COMMENT

It seems apparent from the cases described that the patients who have heart failure in beriberi are those who have mild neurologic signs and a preservation of muscular power. If they are able to carry on normal activities, a burden is placed on the heart, which is already embarrassed by the deficiency of vitamin. This causes a failure of the myocardium. If the nervous system is extensively involved, so that a polyneuritis develops, the patient is unable to carry on normal activities. As a result, the burden of exercise is not placed on the heart and failure does not occur.

It has been pointed out by Aalsmeer and Wenkebach [8] and Stanley [15] that heart failure may occur in patients with beriberi before neurologic signs appear. One also finds supporting evidence of this fact in the papers of Sprawson,[16] Vitug [17] and others. While the presence or

15. Stanley, A.: Beriberi and the Heart, J. Trop. Med. **4**:351, 1901.

16. Sprawson, C. A.: The Heart in Beriberi and the Evidence of the Differential Stethoscope, Indian J. M. Research **9**:625, 1921-1922.

17. Vitug, W.: Some Clinical Aspects of Acute Cardiac Beriberi in Adults, J Philippine Islands M. A. **6**:380, 1926.

absence of neurologic changes is of importance in determining whether or not heart failure will occur, the fundamental mechanism of the heart failure must be explained in another way, since muscular exercise does not cause a normal heart to fail. A number of hypotheses have been put forth to explain this mechanism, and they may be reviewed briefly.

MECHANISM OF HEART FAILURE

Any explanation of the mechanism of heart failure in beriberi must account for two outstanding features: first, the predominance of cardiac enlargement on the right side, and second, the disturbed contractility.

The various hypotheses which attempt to explain these abnormalities may be summarized as follows:

The Vagus Hypothesis.—One of the oldest hypotheses as to the cause of heart failure in beriberi is that it is due to degeneration of the vagus nerves. This hypothesis was proposed when less exact information was had regarding the functions of the vagus. One may say, at present, that there is no evidence that paralysis of the vagus can cause the picture of heart failure seen in beriberi. This is supported by the fact that many patients have heart failure without any evidence of vagal involvement, and when tachycardia develops as a result of paralysis of the vagus with atropine, the heart decreases rather than increases in size.[14] It would seem unlikely, therefore, that vagal paralysis is responsible for either the heart failure or the cardiac enlargement in these patients. This opinion has also been expressed by Stanley,[15] Aalsmeer and Wenkebach, Shimazono and others.

Hypothesis of Respiratory Paralysis.—The hypothesis that heart failure in beriberi results from respiratory paralysis was first proposed by M. Muira.[18] He felt that the hypertrophy of the right side of the heart was due to a retraction of the lungs and to an elevation of the diaphragm and a contraction of the branches of the pulmonary arteries. However, Matsuoka [19] did not find changes in the pulmonary vessels in fatal cases of beriberi. He felt that the dilatation and hypertrophy of the right side of the heart were probably due to the collapse and congestion of the lung that follows hydrothorax, and to the high position of the diaphragm. This explanation fails to account for the presence of heart failure with enlargement of the right side of the heart in the absence of hydrothorax or diaphragmatic paralysis.

The Water Retention or Edema Hypothesis.—The hypothesis that heart failure in beriberi is due to retention of water was recently pro-

18. Muira, M.: Nachtrage zur Pathologie der Kakke, Virchows Arch. f. path. Anat. **117**:159, 1889.

19. Matsuoka, Y.: On the Pathological Anatomy of the Lungs in Beriberi (Kakke), J. Path. & Bact. **20**:191, 1915.

posed by Aalsmeer and Wenkebach.[8] These authors feel that a deficiency of vitamin B leads to a disturbance in metabolism which results in both the skeletal and heart muscles absorbing water. This absorption of water leads to edema of the heart muscle with a resulting disturbance in contractility and heart failure. Wenkebach pointed out that in beriberi there are swelling of the muscles, edema and a disturbance in contractility of the heart muscle, without disturbances in conductivity.

In order to account for the disturbances in contractility without disturbances in conductivity on the basis of edema of the heart muscle, they emphasized the fact that Englemann, De Boer and others have shown that when skeletal or heart muscle absorbs water under experimental conditions, disturbances in contractility result, while conductivity remains normal. Since similar changes occur in the heart in beriberi, and since edema of the muscles is a prominent feature of this disease, they concluded that the fundamental cardiac disturbance is due to absorption of water by the heart muscle.[20]

Wenkebach explained the enlargement of the right side of the heart in the following way. He felt that at the beginning of the illness both sides of the heart are involved equally, but, in any case, when the whole heart fails, the right side is doomed before the left. He explained this, first, by the anatomic difference in the two sides of the heart, the right being weaker than the left, and secondly, by the fact that the right side of the heart must deal with all the blood that returns from the periphery, whereas the left side does not receive more blood than the right side is able to transmit. As a result, the right side is struggling against a greater burden than the left. The more the right side of the heart suffers the better the left becomes, since in myocardial insufficiency the blood finally gets to the right side of the heart, but is only partially transmitted to the left, thus reducing the burden of the left chambers.

Furthermore, he concluded that the latter explanation accounts for the signs seen in beriberi, namely, struggle of the right side of the heart, clear lung fields as shown by x-ray pictures and a small rapid pulse indicating competence of the left ventricle.

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20. Since this paper was written, I have learned of some recent, as yet unpublished, observations which seem to support the view that edema is an important cause of the heart failure of beriberi. Harrison and Pilcher (personal communication to the author) found that edema of the tissues causes increased local blood flow, which would tend to increase the work of the heart. The same authors also found that edema causes a diminution in the buffering power of the tissues, and they believe that this effect may be the physicochemical basis for cardiac "fatigue." From their work it appears that edema, originally an effect of congestive failure, is secondarily a cause of further heart failure. The application of their observations to the condition of the heart in beriberi is obvious. The clinical observations reported in this paper seem both to confirm and be confirmed by the experimental observations of Harrison and Pilcher.

Mebius [21] supported the edema hypothesis and went even further. He was of the opinion that a deficiency of vitamin B produces a disturbance in the osmotic pressure of the anisotropic contractile substance of the heart muscle, and that this leads to cardiac weakness. He supported this hypothesis by recording his observations in the hearts of three patients dying of beriberi. The longitudinal striations of the heart muscle were distinct, whereas the cross striations were indistinct and there was an intercellular edema. He compared these observations with the changes that occur in a strip of muscle when it is allowed to absorb water. In support of the argument that these changes are not due to degeneration of the nerves, he stated that many cases of beriberi in the acute stage do not show degeneration of the nerves at necropsy. One may summarize the edema hypothesis by saying that the fundamental disturbance in beriberi is due to absorption of water by the heart muscle, causing defective contractility and heart failure.

On the whole, this explanation of the cardiac disturbance in beriberi seems reasonable. How, then, does muscular exercise exaggerate this condition? This problem has been studied recently by Inawashiro and Haynasaka,[22] who found that patients with beriberi have an increased circulatory minute volume, an increased amount of lactic acid in the blood, and a diminished carbon dioxide content of the venous blood while they are at rest. Following muscular exercise, there is a further increase in the circulatory minute volume, and in the amount of lactic acid in the blood, a further decrease in the carbon dioxide content of the venous blood and an increase in the systolic, and a decrease in the diastolic, blood pressure. They concluded from their observations that the fundamental factor in vitamin B deficiency is a disturbance in muscle metabolism with a resulting acidosis, and that this disturbance is exaggerated by muscular exercise. They were of the opinion that the increased circulatory minute volume together with the paralysis of the respiratory muscles and the acidosis, accounted for the enlargement of the right side of the heart. They attributed the increased circulatory minute volume to a relaxation of the peripheral vessels, due in part to vasomotor paralysis and in part to acidosis.

In summarizing the observations on the mechanism of cardiac insufficiency in beriberi, it might be said that a deficiency in vitamin B causes changes in the heart muscle. These changes are characterized by cardiac enlargement and deficient contractile power. The conductivity is altered slightly in some cases, but as a rule it remains normal.

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21. Mebius, J.: Oedemtheorie der Beriberi und physiologische Wirkung des Vitamine B, Virchows Arch. f. path. Anat. **271**:422, 1929.

22. Inawashiro and Hayasaka: Tohoku J. Exper. Med. **12**:1 (Dec. 30) 1928.

Muscular exercise plays a tremendous rôle in the course of the disease. If the patient is not disabled by polyneuritis and performs muscular work, cardiac insufficiency results. If polyneuritis is present, the myocardium is usually protected from the increased burden of muscular exercise, and cardiac failure does not appear.

This type of heart failure emphasizes two points of importance in the study of any form of heart disease, namely, the rôle of nutrition and the rôle of exercise.

Recently Smith [23] emphasized the importance of a proper diet in the treatment of heart disease. The results he obtained following the treatment of patients with heart failure with diets of high carbohydrate value are suggestive that a proper dietary regimen plays a part in the recovery of many. Certainly in the form of heart failure under discussion a proper diet is absolutely essential for recovery. This is well illustrated by the patients in whom prompt recovery took place following the administration of an adequate diet and yeast without the giving of digitalis.

The rôle of muscular exercise in the production of any form of heart failure is of importance. This subject was recently reviewed by Barr.[24] He emphasized the importance of muscular exertion in producing conditions which result in the symptoms and signs of heart failure. In no type of heart disease is this fact better illustrated than in the cases described. If the patient is unable to carry on exercise owing to peripheral neuritis, cardiac insufficiency does not appear.

SUMMARY

A group of patients with beriberi were studied with particular reference to the cardiovascular system. It was clearly demonstrated that the patients who develop cardiac insufficiency are those who have the least involvement of the nervous system. The hypotheses that have been advanced in explanation of the mechanism of heart failure in this disease were reviewed and the mechanism discussed. The importance of diet and exercise in the management of heart disease was emphasized.

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23. Smith, F.: Diet and Theophylline in Cardiac Failure, J. A. M. A. **91**: 1274 (Oct. 27) 1928.

24. Barr, D. P.: Exercise in Cardiac Disease, J. A. M. A. **91**:1354 (Nov. 3) 1928.

CHRONIC GLOMERULONEPHRITIS WITH LIPOID CHANGES

A REPORT OF AN ILLUSTRATIVE CASE STUDIED FROM THE ONSET UNTIL DEATH FIVE YEARS LATER *

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The clinical and morphologic features of chronic glomerulonephritis with lipoid changes are fairly well known. Often, however, such patients are studied for a short time only and during one period of the disease, usually at an advanced stage, when there are unmistakable evidences of well developed renal failure. There is, as a result, a disconnected clinical picture and a lack of appreciation of the proper sequence of events. The continuous study of a patient over a longer time usually furnishes some information that would be impossible to gather from shorter periods of observation. The illustrative case presented here was studied from the onset of the illness until death five years later. My object in this paper is to analyze the following features illustrated by the study of this case:

1. The major clinical syndromes are discussed; and it is shown that not all appear at the same time, but come and go with great irregularity. Some syndromes develop and dominate the clinical picture for a while and then fade away, either to return at a later date or never to return.

2. Hypercholesterolemia is considered, and its relationship to lipoid deposits in the kidneys and to arteriosclerosis is emphasized.

3. The changes found in the arteries and arterioles of the internal organs and skeletal muscles are described, and especial attention is given to changes in the arterioles of the kidney.

REPORT OF CASE

History.—A white boy, aged 12 years, was first taken sick in January, 1924. There was no history of any infectious diseases of childhood. He had had tonsillitis, and the tonsils were removed when he was 7 years old. The present illness began with a moderate generalized edema, vomiting and headache. The urinalysis revealed a mild albuminuria with few cellular elements. The blood pressure was normal; no other tests were done at that time. The edema disappeared rapidly, and within a week he felt fairly well. On March 9, 1924, after his mother died, he was admitted to the Milwaukee County Home for Dependent Children. On entrance the urine was free from albumin, and the blood pressure

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was normal. He remained in good health until Nov. 6, 1925, when he was taken to the Milwaukee County Hospital because of cervical adenitis and generalized edema, most prominent about the face, as presented in the accompanying table.

At the examination on entrance to the hospital, the boy was well developed, with a butter-yellowish tinge to the skin. Urinalysis showed the albumin and cellular elements usually found in nephritis. A careful search for doubly refracting lipoids with the polarizing microscope revealed none. The chemical examination of the blood showed nothing abnormal, except for a well developed hypercholesterolemia. Renal functional tests disclosed normal results. The cardiovascular system was normal. There was a moderate secondary anemia. The eyegrounds were normal.

Within a few weeks the edema and adenopathy had gone, and the patient felt well. The urine continued to have albumin in it, while the cellular elements gradually diminished until only a few cells and casts were found. The blood pressure remained normal; there was a slight improvement in the anemia, although the red cell count continued to be well under normal.

From the time of entrance to the hospital on Nov. 6, 1925, until Sept. 8, 1926, this patient was under continuous study. Renal function tests, blood counts, determinations of blood pressure and urinalyses were done as a routine.

Doubly refracting lipoids were sought for almost daily in the urine, and were first found on July 18, 1926. The cholesterol of the blood remained above 300 mg. per hundred cubic centimeters throughout the illness. The edema did not return until later in the course of the disease. The boy was dismissed from the hospital on Sept. 8, 1926, and sent back to school.

On Sept. 28, 1926, he developed a mastoid infection and came back to the hospital in a serious condition. He underwent a successful mastoid operation. During this crisis, the blood pressure remained normal, as did the blood nitrogen and other renal functional tests. The urine showed albumin 3 plus. Many hyaline and granular casts, red blood cells, pus cells and doubly refracting lipoids were also present. A profound anemia developed, the red cell count dropping to 1,600,000. No edema developed. Within a month after operation the blood count was 3,400,000, where it remained in spite of further treatment. The urine cleared up except for the presence of albumin 2 plus, a few cellular elements and many doubly refracting lipoids. On Dec. 10, 1926, the patient was dismissed from the hospital. In general, he appeared to be in good health and aside from the anemia, a mild albuminuria and a hypercholesterolemia, the examination and tests revealed no abnormalities.

During the early part of 1927, biweekly examinations were done in the outpatient department, and the boy appeared healthy and normal. The urine contained albumin and doubly refracting lipoids. The blood pressure remained normal; the hypercholesterolemia and anemia persisted. On or about April 1, a systolic murmur was heard for the first time over the aortic area. This murmur was transmitted down along the left sternal border and was heard distinctly in the mitral area. Its quality was soft and not unlike a hemic murmur. During the remainder of the course of the disease, this murmur was studied. It became louder, but the area of transmission did not change.

In September, 1927, the boy was symptomless, although the blood pressure had risen (for the first time) to 148 systolic; 100, diastolic. The only other change found was a definite defect in the renal concentration ability, elicited by the dilution concentration test of Volhard. The MacLean urea concentration test also revealed evidences of the defect. He continued to go to school.

Summary of Data in Case Report

	Urine							Blood Chemistry					Function				
Year	Albumin	Oliguria	Hypostheuria	Red Blood Cells	White Blood Cells	Casts	Lipoids, Doubly Refracting	Urea Nitrogen	Creatinine	Cholesterol	Carbon Dioxide Combining Power of Plasma	Red Blood Cell Count	Phenolsulphonphthalein	Dilution and Concentration Tests	Blood Pressure	Edema	Comment
3/16/24	2+	0	0	0	2+	0	...	....	...	...	..	.....	..	.....	115/ 80	2+	
12/ 2/24	1+	0	0	0	0	0	...	....	...	...	..	.....	..	.....	110/ 70	0	
5/12/25	2+	0	0	0	0	0	0	....	...	...	..	.....	..	.....	115/ 80	0	
11/ 6/25	4+	2+	0	2+	2+	Granular, 2+	0	14.9	2.0	327	..	3,500,000	70	1.004-1.026	118/ 70	4+	Eyegrounds normal
12/31/25	1+	0	0	1+	1+	Granular, 1+	0	11.2	1.6	390	..	.....	65	1.002-1.022	110/ 65	0	
4/ 4/26	3+	0	0	0	0	0	0	12.9	1.4	387	52	3,700,000	70	1.006-1.021	120/ 85	2+	Edema for 1 week
5/25/26	2+	0	0	1+	2+	Granular, 1+	0	14.3	1.8	333	..	.....	60	.....	115/ 75	0	
7/18/26	3+	0	0	0	1+	Granular, 1+	2+	16.2	1.5	342	..	.....	75	1.004-1.020	120/ 70	2+	Doubly refracting lipoids found for first time
9/ 8/26	2+	0	0	0	1+	0	3+	15.1	1.3	361	..	3,800,000	65	.....	115/ 60	0	Dismissed from hospital
9/28/26	4+	2+	1+	3+	3+	Granular and hyaline, 3+	4+	16.7	2.2	410	45	2,250,000	65	.....	142/ 90	0	Had mastoid operation
12/10/26	2+	0	0	1+	1+	0	4+	10.4	1.8	350	..	3,650,000	55	.....	145/ 95	0	Dismissed from hospital
1/15/27	2+	0	0	1+	1+	0	3+	15.3	2.1	347	58	.....	65	.....	130/ 80	0	
6/ 7/27	3+	0	0	1+	1+	0	3+	16.2	1.3	325	..	3,800,000	55	1.006-1.022	125/170	3+	Edematous for 1 week
9/ 5/27	2+	0	0	0	2+	0	3+	10.6	1.9	371	..	.....	65	1.008-1.015	145/ 90	0	Going to school
11/11/27	3+	2+	2+	3+	3+	Granular, 2+	4+	18.2	2.5	305	42	4,080,000	60	1.010-1.015	160/100	2+	Developed bronchopneumonia
12/ 2/27	3+	2+	3+	2+	2+	Granular, 3+	3+	20.1	2.4	314	..	3,100,000	65	.....	165/ 95	0	Meningococcic meningitis
12/23/27	3+	0	2+	1+	1+	Granular, 1+	4+	12.6	1.2	309	..	.....	50	1.005-1.012	150/100	0	
1/15/28	3+	0	2+	1+	1+	Granular, 1+	3+	15.0	2.2	365	50	3,680,000	65	1.008-1.012	190/120	0	Occasional headache only complaint
2/ 2/28	3+	0	2+	2+	2+	Granular, 2+	3+	17.4	2.0	322	..	.....	70	.....	230/150	1+	Convulsive uremia; albuminuric retinitis when seen for first time
3/15/28	1+	1+	2+	1+	0	0	3+	12.0	1.5	360	58	3,610,000	55	1.009-1.013	210/120	0	Appeared very well
5/ 2/28	1+	0	3+	1+	1+	Granular, 1+	4+	20.2	2.6	315	..	.....	40	1.008-1.012	200/125	0	Weak and felt poorly
8/21/28	3+	1+	3+	2+	2+	Granular, 2+	3+	18.0	2.6	380	37	3,450,000	35	1.005-1.009	220/120	...	
11/ 7/28	3+	2+	3+	3+	3+	Granular, 2+	4+	30.1	2.9	250	..	.....	20	1.007-1.011	210/130	...	
12/15/28	3+	3+	3+	3+	3+	Granular, 3+	4+	35.2	3.1	160	23	3,220,000	15	.....	160/120	...	Stupor and twitching set in; died Dec. 20, 1928

About Nov. 1, 1927, slight edema of the face and ankles appeared with no other noteworthy changes. On November 11, he was taken ill with bronchopneumonia, and was removed to the hospital. The blood pressure was found to be elevated to 160, systolic; 110, diastolic, and the abnormal urinary condition was increased. Renal concentration tests disclosed a depression in function, while the phenolsulphonphthalein test and the blood nitrogen were normal. Hypercholesterolemia was present. Within a few weeks, the pneumonia cleared up, the nephritic condition changing little.

Following the patient's recovery from pneumonia, he developed cerebrospinal meningitis (epidemic type). On Dec. 2, 1927, during the course of meningitis, the abnormal urinary condition increased markedly while no retention of blood nitrogen or edema was noted. The recovery from meningitis was complete by Jan. 2, 1928. Aside from the anemia, the general condition improved rapidly. The blood cholesterol never dropped below 300 mg. per hundred cubic centimeters during any of the illnesses. The general condition of the patient steadily improved, and on February 1, the cells had practically gone from the urine and only moderate quantities of albumin were present. There was a gradual rise in blood pressure until by this time it measured 250, systolic; 130, diastolic. Aside from the increasing blood pressure, it appeared that the nephritis was becoming quiescent. The ophthalmoscopic examination, which had shown normal results prior to this time, disclosed a considerable choroidal exudate around the disks, but no hemorrhages were found. Progress seemed satisfactory except for the hypertension until February 25, when he developed a typical attack of convulsive uremia. This was controlled by intravenous injections of 10 per cent magnesium sulphate solution and hot packs. The urinary symptoms had increased, while the blood nitrogen and the phenolsulphonphthalein test remained normal. The eyegrounds on the day following the convulsions showed hemorrhages in the retina. During the following four months, rapid improvement was noted. The urinary condition was reduced considerably, and he was entirely free from symptoms except for headache which came and went at infrequent intervals. The albuminuric retinitis and anemia persisted.

In the summer of 1928, many changes for the worse developed. There was an increase in all pathologic urinary elements; the urinary concentration ability decreased, and there was a reduction in the phenolsulphonphthalein output. No great increase, however, was found in the blood nitrogen. A definite fall of the blood cholesterol appeared, and the blood pressure remained highly elevated. The patient slowly declined during the fall of 1928, and by December was confined to bed because of weakness, headache and gastro-intestinal disturbances. Coma with twitchings but with no convulsions followed. The blood nitrogen never rose to a high figure. Bronchopneumonia of the terminal type helped to shorten life. He died on Dec. 20, 1928, of uremic coma and bronchopneumonia.

Abstract of Autopsy Report.—The body was well developed and nourished; the skin and visible mucous membranes were pale with a tinge of yellow. Edema of the ankles and face was found, and the abdominal cavity was filled with a clear, serous fluid. Areas of bronchopneumonia were found in the left upper and lower lobes. The liver was enlarged and engorged with blood. The spleen was enlarged, measuring 15 by 17 by 4 cm. Bloody fluid was present in the stomach, and the mucous membrane showed many petechial hemorrhages.

Examination of the heart disclosed the following: It was enlarged, measuring 11 cm. at the base and the distance from apex to base was 12 cm. The valves were intact. The anterior mitral cusp contained on its aortic aspect a few yellowish patchy deposits. The aorta in its ascending portion and arch had rich

deposits of this yellowish, fatty material and presented a picture of atherosclerosis. Fatty degeneration was found in the heart muscle.

The right kidney weighed 182 Gm.; the left, 197 Gm. Embryonal lobulations were found in both. When the capsule was stripped, the surface of the kidney was seen to be richly speckled with distinct, small, yellowish crystals which were found to be fat. On the cut surface, the markings were found to be distinct. The cortex and columns of Bertini were extensively speckled with flakelike yellowish fatty deposits. The renal arteries and the arteries seen on the cut surfaces of the kidneys were found to have undergone profound arteriosclerotic changes.

Microscopic Examination.—All sections were stained and studied with hemotoxylin-eosin, van Gieson's, Weigert's elastic tissue stain, sudan III and Giemsa's stain. Polariscopic examinations were done when fat was found.

The aorta (section of a yellow patch) showed extensive hyperplasia of the elastic tissue of the intima. Fatty degeneration of the intima was pronounced, and there was extension of fat into the media. The fatty substance showed evidence of confluence and formed spaces in the intima filled with cellular débris. Some of the fat was doubly refracting and was considered to be cholesterol ester. In the intima, the connective tissue was considerably increased. The processes in the intima had the appearance of atheromatous cavities before the stage of ulcer formation. In the aortic wall, the arterioles had thickened walls. This thickening was due to hypertrophy of the muscular tissue of the media.

A picture of chronic passive congestion was found in the spleen. The vessels appeared to be normal. No fat was found.

There were no demonstrable changes in the intimal layers of any of the vessels of the skeletal muscle. The medial coat of the arterioles and smaller arteries showed practically no change.

With sudan III, considerable fat was seen in the periphery of the lobules of the liver. Much of it doubly refracted polarized light. The walls of the liver arterioles in places were slightly thickened by virtue of fatty degeneration of the intima. The media was not increased.

There was a decided increase in the interstitial fibrous tissue of the kidneys. Many glomeruli were completely fibrosed; others were enlarged and showed an increase in cellularity. Occasionally, a glomerulus was seen in which some loops were fibrosed and adjacent loops were thrombosed. Characteristic crescent formations were numerous. Almost universally, Bowman's capsules were thickened with fibrous tissue. No evidences of acute inflammatory processes were present. The epithelium of the convoluted tubules was everywhere diseased. Fatty and granular degeneration with swelling and various stages of disintegration of the epithelial cells was the chief change. In places no lining epithelial cells were found, the basement membrane being covered only by cell débris. With fat stains the epithelium of the convoluted tubules was found to be loaded with fat. A great deal of fat was also present in the interstitial tissue. Practically all of this fat doubly refracted polarized light and was considered, therefore, to be cholesterol ester.

The arteries and arterioles of the kidney were universally damaged. The renal, arcuate and interlobular arteries for the most part had undergone definite arteriosclerotic changes. The media was reduced in size, and fatty degeneration characterized the swollen intimal tissues the elastic tissue of which had become hyperplastic. In some of the interlobular arteries, the media was thickened, and the intima increased due to connective tissue proliferation, no fatty changes being seen in them. At the boundary zone between the swollen intima and thickened media,

vacuoles were found in some areas, and empty spaces were seen also, scattered throughout the media.

The renal arteriolar walls were thickened everywhere, and the vascular lumina was almost obliterated in some places. Two definite types of changes were found occasionally in the same microscopic field. In some arterioles the media was hypertrophied, and the intima was either intact or was thickened from a proliferation of connective tissue; in others, the media was reduced and the intima was thickened with fatty degeneration or with increase of the connective tissue. No necrotic changes were found in the walls.

COMMENT

The Clinical Syndromes.—The changeableness of the symptoms of chronic nephritis often leads to confusion in the proper interpretation of the clinical picture at some stages of the disease. This variability of the symptoms is well represented in the illustrative case reported here. The symptoms were seen to occur at times in such combinations as to suggest the diagnosis of lipoid nephrosis; at other times, the symptom arrangement would lead one to suspect malignant hypertension. For the purpose of clarity, it is well to classify the leading symptoms into five syndromes as follows: (*a*) urinary; (*b*) nitrogen retention; (*c*) hypertension; (*d*) edema and (*e*) uremic.

All of the syndromes except the nitrogen retention were seen to appear at one time or other during the course of the disease. In some periods of the disease, all the syndromes except the nitrogen retention were present at one time; and then one by one they disappeared, either to recur later or never to return at all. On June 7, 1927, the urinary manifestations, the edema, and hypercholesterolemia with no hypertension, hematuria or nitrogen retention, produced the clinical features resembling lipoid nephrosis; while in March, 1928, the marked hypertension and a severe retinitis without nitrogen retention and edema constituted a clinical picture resembling malignant hypertension, as shown in the accompanying table.

During the entire course of the disease, the nitrogen retention syndrome was absent. When uremia developed on Feb. 2, 1928, there was no retention of nitrogen, although the uremia was convulsive in nature. At the end of the course, in December, 1928, twitching developed, but no convulsions followed; the patient had the clinical picture of true uremia, yet only slight nitrogen retention was present.

The renal function tests were of interest in that the phenolphthalein was excreted in a normal fashion throughout the course of the disease until toward the end. The earliest sign of impairment of renal function was elicited by the concentration and dilution test of Volhard. No impairment was noted until January, 1928, in the fifth year of observation. It appears probable, therefore, that nephritis must be fairly well advanced, in some cases at least, before the ordinary renal function tests

are of much value in the study of the condition. It emphasizes the inadequacy of the usual renal function tests in detecting early impairment. Of all the syndromes, the urinary was the most constant. The urine was never normal from the onset to the end. It seems fair to suppose that of all the tests and measurements, the close study of the urine, for practical purposes, is the most instructive and important.

The Hypercholesterolemia and the Lipoid Deposits in the Various Organs.—The hypercholesterolemia in this case appeared to antedate the doubly refracting lipoid deposits in the kidney and aorta. This is assumed to be the case because the lipoids were not found in the urine until at least two years after a definite hypercholesterolemia had become established. It was found in animal experimentation (unpublished at present) that lipoid deposits in the renal tubular epithelium are followed shortly (in from ten to fifteen days) by lipoids in the urine. Judging from the data presented, it would seem that a defective fat metabolism was a primary factor and the lipoid deposits in the kidney and blood vessels were results of a combination of forces, one of them being a hypercholesterolemia. It has become fairly well established in the minds of many that lipoid nephrosis is primarily a disturbance in cholesterol and protein metabolism followed by morphologic changes in the kidney epithelium with subsequent deposits of lipoids in the renal tissue. This theory is subscribed to by many observers, including Munk,[1] Lowenthal,[2] Epstein,[3] Fahr,[4] Kollert and Finger[5] and others. The nature of the factors producing hypercholesterolemia is not known. It is undecided at present whether or not the factors that cause pure lipoid nephrosis are the same as those responsible for the nephrotic features of some cases of glomerulonephritis. Elwyn[6] emphasized the importance of glomerular damage in the production of lipoid nephrosis. He believed that the injury to the glomerulus was the primary factor in the disturbance. Stepp[7] also considered the damage of the renal epithelium to be the chief cause of the hypercholesterolemia. From time to time

1. Munk, F.: Pathologie und klinik der nierenerkrankungen, Vienna, Urban and Schwartzenberg, 1925.

2. Lowenthal, K.: Zur Frage der Lipoid Nephrose, Virchows Arch. f. path. Anat. **261**:109, 1926.

3. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Method for Its Alleviation, Am. J. M. Sc. **154**:638, 1917.

4. Fahr, T.: Beitrage Zur Frage der Nephrose, Virchows Arch. f. path. Anat. **239**:32, 1922.

5. Kollert, V., and Finger, A.: Ueber die Beziehungen der Nephritis zum Cholesterin (Lipoid) Stoffwechsel, München. med. Wchnschr. **65**:816, 1918.

6. Elwyn, Herman: The Pathogenesis of Lipoid Nephrosis, Arch. Int. Med. **38**:346 (Sept.) 1926.

7. Stepp, W.: Ueber den Cholesteringehalt des Blutes bei verschiedenen Formen der Bright'schen Krankheit, Deutsches Arch. f. klin. Med. **127**:439, 1918.

it has been advocated that the main factor in nephritis is not the kidney damage but some extrarenal disturbances which result in kidney damage. Graves,[8] in 1831, was unwilling to accept Bright's interpretation of albuminous urine as indicative of primary renal disease. He regarded the albuminuria as a cause and the pathologic changes in the kidney as the result of it. Graves considered nephritis as a general disturbance and believed that the liver or some other organs were primarily responsible for the condition. A similar theory has been expressed and experimental data submitted to substantiate it by Andrews, Thomas and Welker.[9] They contended that there are changes in the osmotic equilibrium associated with alterations in the mineral salt balance which induce increased tissue permeability. This allows passage of tissue proteins into the blood which are foreign to the circulation, and they are excreted. They suggest that nephritis is comparable to diabetes in the sense that protein metabolism is interfered with by some means, so that oxidation is incomplete and the processes stop at a stage where the products of nitrogenous metabolism are toxic and are eliminated. That hypercholesterolemia in itself is not sufficient for the production of lipoid deposits in the kidney and other tissues was proved by Chalatow.[10] He showed that when the cells are injured a slight rise in blood cholesterol is sufficient to cause deposits of lipoid in the injured cells.

The relationship of the lipoid changes in the kidney to the edema of nephritis has been reported elsewhere [11] and therefore will not be discussed here. In the autopsy report, it is seen that a well developed arteriosclerosis was found in the ascending portion of the aorta and an arteriosclerotic plaque was present on one of the mitral cusps. The murmur that was first heard about April 1, 1927, was undoubtedly produced by the lesion on the mitral valve. In the presence of a long standing hypercholesterolemia, it is not unusual to find these lipoid deposits in the valve. In another case, one of pure lipoid nephrosis, reported by Murphy and Warfield,[12] a similar picture of arteriosclerosis was found in the aorta, and the aortic leaflet of the mitral valve showed a similar lesion as described here. The development of a profound

8. Graves, R., quoted by Bartels, in Ziemssen's Cyclopedia of Practice of Medicine, 1877, p. 15.

9. Andrews, Edmund; Thomas, William A., and Welker, William F.: Albuminuria in the Mechanism of Detoxification, Arch. Int. Med. **43**:139 (Jan.) 1929.

10. Chalatow, S. S.: Die Anisotrope verfettung in Lichte der Pathologie des Stoffwechsels, Jena, Gustav Fischer, 1922.

11. Murphy, Francis D.: Chronic Nephritis With and Without Edema: A Study of Cholesterol in These Conditions, J. Clin. Investigation **5**:63, 1927.

12. Murphy, Francis D., and Warfield, Louis M.: Lipoid Nephrosis, Arch. Int. Med. **38**:449 (Oct.) 1926.

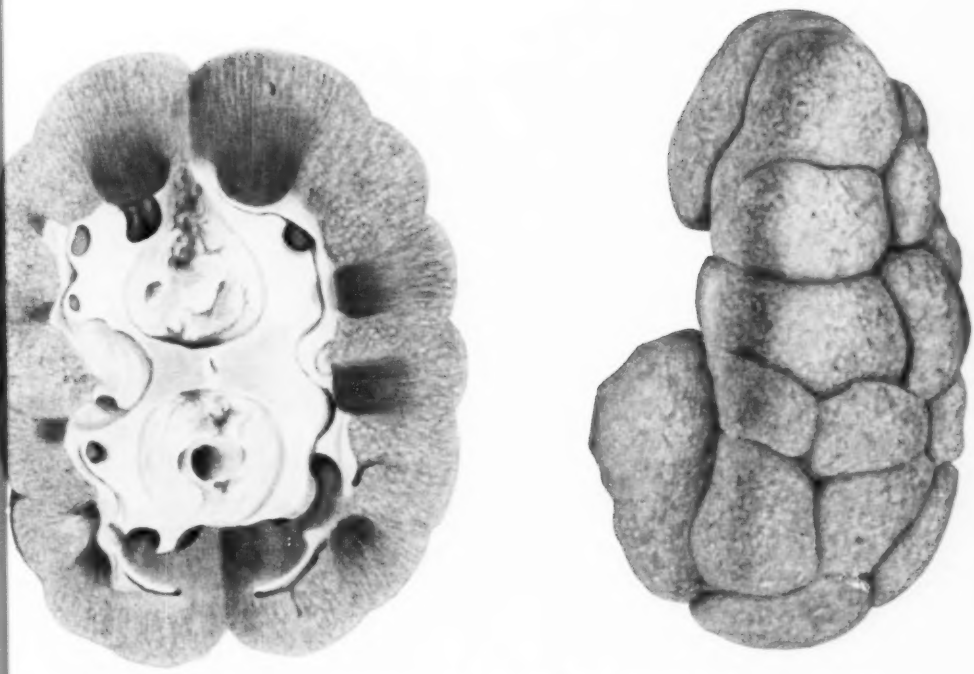

Fig. 1.—At left, right kidney, showing the flaky yellowish deposits of lipoids distributed uniformly throughout the organ; at right, the surface of the same specimen. Water color painting.

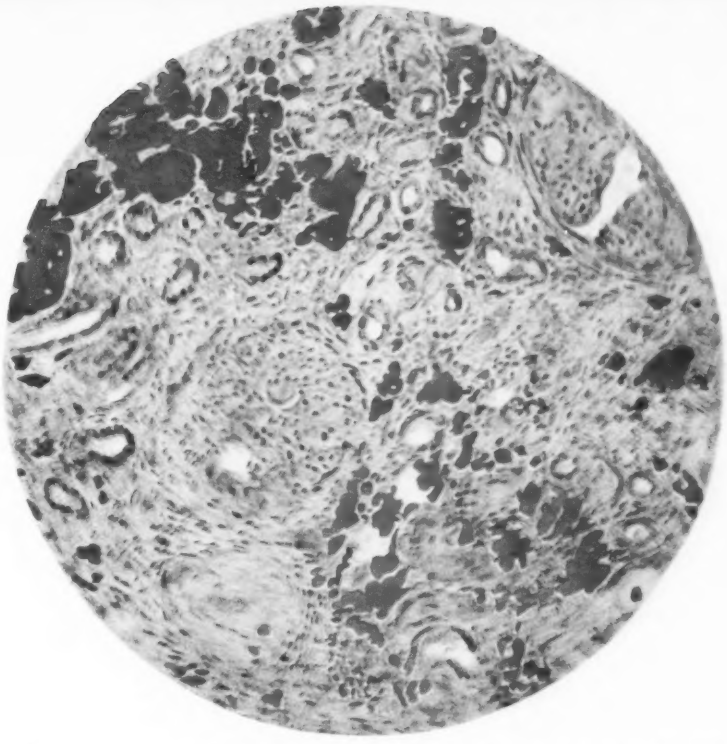

Fig. 2.—The extensive deposits of lipoid substances in the tubular epithelium and in the interstitial tissue. Hand colored photomicrograph.

Fig. 3.—Section through a yellowish plaque in the aorta demonstrating the deposits of lipoid substances in the intima. Hand colored photomicrograph.

arteriosclerosis in these young patients who have diseases characterized by hypercholesterolemia leads one to suspect that a high fat diet, especially one rich in cholesterol fat, may be more injurious than is commonly supposed. Joslin [13] questioned the advisability of giving a diabetic patient a diet rich in cholesterol, especially if the patient has a hypercholesterolemia or signs of arteriosclerosis.

These clinical observations on the relationship of hypercholesterolemia are in accordance with the experimental work done on this subject. Ignatowski [14] produced an infiltration of fat in the intima by feeding rabbits with egg yolk. In 1910, Stuckey [15] fed rabbits with meat juices, egg albumin and milk, and no changes occurred. He then fed rabbits with egg yolk, and a fatty infiltration of the intima developed. He said that the changes were similar to those found in human arteriosclerosis. Stuckey tried many different animal and vegetable fats but no intimal changes occurred in the aorta, except in those fed with egg yolk and brain substance. Anitschkow and Chalatow,[16] after feeding brain substance and egg yolk to rabbits, recognized that the lipoid deposits in the intima doubly refracted polarized light and concluded that the fatty deposits were cholesterol esters. They then fed pure cholesterol and produced a hypercholesterolemia and found lipoid deposits in nearly all of the parenchymatous organs of the body. In 1924, Anitschkow,[17] in an article summarizing his work on this subject, stated that the hypercholesterolemia was the main factor in development of arteriosclerosis. He observed that in experimental work in internal parenchymatous organs, a universal deposit of lipoids occurred, while in the human being only the larger vessels had lipoids in their walls; and furthermore, that an extensive hypercholesterolemia must be present to cause lipoid deposits experimentally, while in human beings extensive lipoid deposits form without a high degree of hypercholesterolemia. Anitschkow attempted to produce a selective lipoid deposit in the aorta without much deposit in the liver, kidney and other organs. The results were as follows: (1) the arteriosclerotic changes were hastened when the hypercholesterolemia

13. Joslin, Elliott P.: The Ten-Year Diabetic. What He Is. What He Should Be. How to Make Him So, Am. J. M. Sc. **175**:472, 1928.

14. Ignatowski, A.: Zur Frage ueber den Einfluss der animalischer Nahrung auf der Kaninchenorganismus, Berichte der Kaiserlichen militär-mediz., Akademie zu St. Petersburg, 1908, p. 16.

15. Stuckey, N. W.: Ueber die Veränderungen der Kaninchenaorta bei der Fütterung mit verschiedenen Fettsorten, Centralbl. f. Allg. path. u. path. Anat. **23**:910, 1912.

16. Anitschkow, N., and Chalatow, S.: Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Endstehung einiger Pathologischer Prosesse, Centralbl. f. Allg. path. u. path. Anat. **24**:1, 1913.

17. Anitschkow, N.: Zür Aetiology der Atherosklerose, Virchows Arch. f. path. Anat. **249**:73, 1924.

was combined with some mechanical or toxic factors; (2) animals (rabbits) fed on small doses of cholesterol for two and one-half years developed no hypercholesterolemia, but a moderate degree of arteriosclerosis was found and the other organs were normal. He stated that lipoids were deposited where the intima was damaged, and that an abnormal cholesterol metabolism plus some strain (mechanical or toxic) brought on arteriosclerosis.

Aschoff [18] differentiated between the atherosclerosis seen in the ascending, the summit, and the descending periods in the life of a vessel. The ascending period in the life of the vessel ends with the thirty-second year; the summit is from then until the forty-fifth year, which marks the commencement of the descending period. In discussing the atheromatosis of puberty, he emphasized that the essential factors in this early form are a swelling of the inner layers of the intima, with a diffuse minute granular deposition of fat beginning in the depths of the stria elastica terminalis, and extending further and further toward the surface. Aschoff stated that the atheromatous spots develop in the regions of the vascular system which are under great physiologic strain. He added that there is a second factor that must be present before the atheromatous spots may appear. This, he said, is a sufficient concentration of lipoids, especially cholesterol esters, in the plasma. From a plasma of low concentration of cholesterol no deposition of lipoids will occur, even though mechanical conditions are favorable.

In the case reported here, the forces necessary for the production of lipoid deposits were present. To what extent the various factors, such as the infections and hypertension, influenced the lipoid changes is difficult to state. The arteriosclerosis and lipoid deposits in the aorta and the kidneys appear to have developed independently of the hypertension.

The Arteriolar Changes.—The morphologic changes in the arterioles of the parenchymatous organs have been studied extensively in recent years. Lohlein [19] concluded that arteriolar disease in the secondary contracted kidney may be present, but at times may be absent. He stated that two types of changes may be seen in the afferent glomerular arteriole. First, a dilatation with thinning of the vessel may result from degeneration and necrosis of the arteriolar wall. The necrosis may extend into the loops of the glomerulus leading to an infarcation of those loops. Second, hyaline rings may form in the wall of the interlobular artery as well as the afferent arteriole. This hyaline process is associated with a lakelike dilatation of the vessel, usually near the hilum of

18. Aschoff, Ludwig: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.

19. Lohlein, M.: Ueber Schrumpfnieren, Beitr. z. path. Anat. u. Allg. Path. **63**:57, 1916.

the tuft. When the changes are severe, according to Lohlein, a thrombus may develop leading to a hemorrhagic infarct in the glomerulus.

Branch and Linder [20] reported observations on the microscopic examination of the vessels of the kidney and other organs in ten cases of chronic nephritis. Three cases were in children of 3 years, whose parenchymatous organs showed no arteriolar change. In one case,

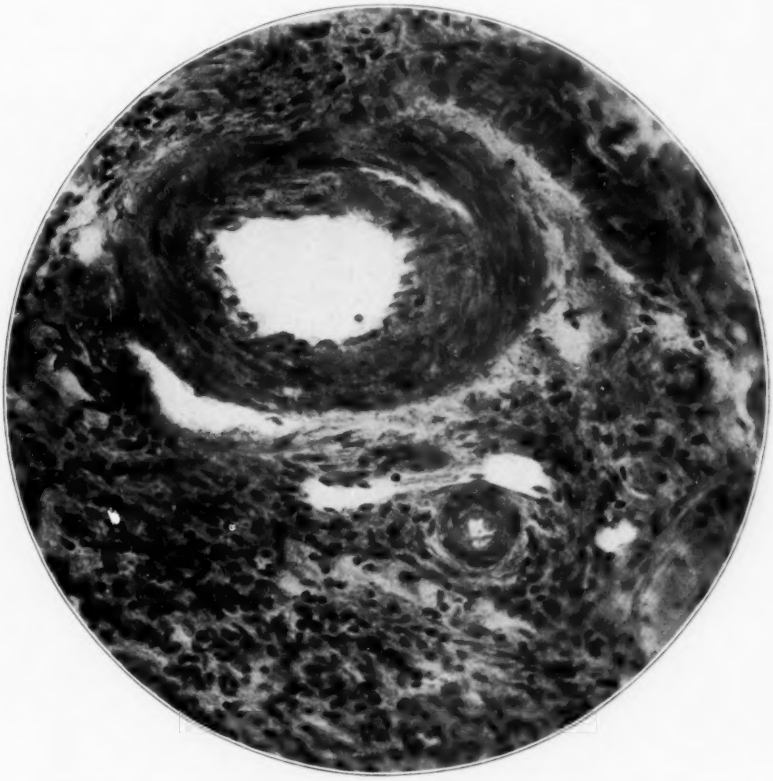

Fig. 4.—A section of kidney showing proliferative changes in the intima of a smaller artery and arteriole; × 700.

nephritis had existed for months but no arteriolar thickening occurred. In the six remaining cases, the arterioles and their parent arteries of the parenchymatous organs were thickened, and the intima had undergone

20. Branch, Arnold; and Linder, Geoffry C.: The Association of Generalized Arteriolar Sclerosis with High Blood Pressure and Cardiac Hypertrophy in Chronic Nephritis, J. Clin. Investigation **3**:299, 1926.

fatty degeneration and the media was thinned. The authors stated that the arterioles of skeletal muscles were unaffected.

Fishberg [21] found that the arteriolar lesions of glomerulonephritis were of four histologically and pathologically distinct varieties:

1. Acute necrotizing arteritis was found in patients dying of acute diffuse glomerulonephritis.

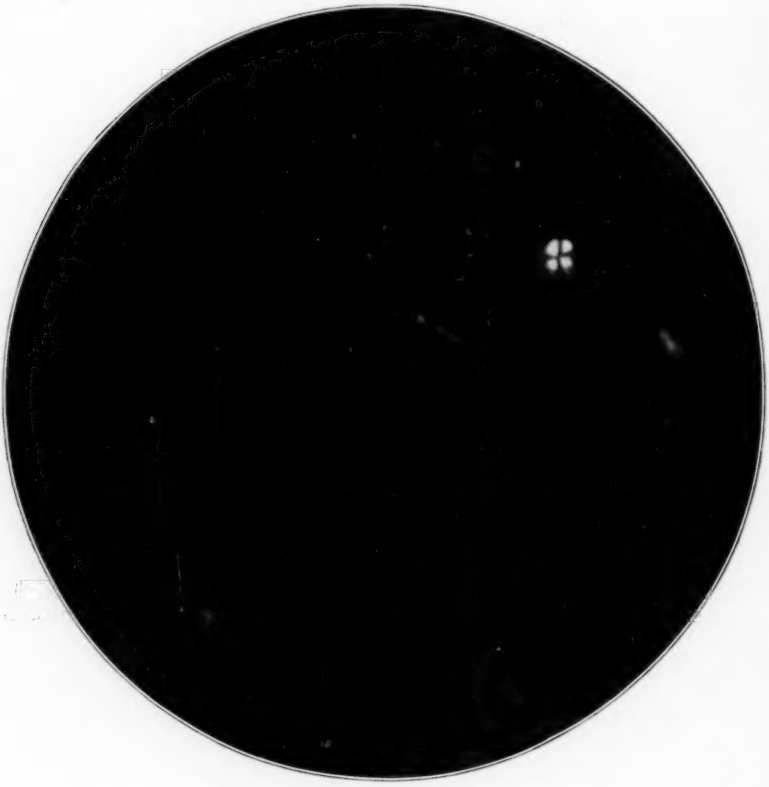

Fig. 5.—Unstained section observed under crossed Nicol's prisms, illustrating the doubly refracting nature of the lipoid deposits; × 800.

2. Endarteritis obliterans was present in seventeen of twenty-nine cases of chronic diffuse glomerulonephritis.

3. Arteriosclerosis, similar in histology and distribution of the lesions to that found in essential hypertension, was present in twelve cases of secondary contracted kidney.

21. Fishberg, A. M.: The Arteriolar Lesions of Glomerulonephritis, Arch. Int. Med. **40**:80 (July) 1927.

4. Muscular hypertrophy in the media of renal arterioles was well marked in many cases of chronic glomerulonephritis.

He stated that the arterioles of the skeletal muscle and skin are usually unimpaired. In his study he found these various morphologic changes at times in the same kidney, and he attributed them to the action of different forces. He concluded that the degenerative or arteriosclerotic changes were dependent on the hypertension, while the endarteritis obliterans, he assumed, was produced by the blocking of the blood flow subsequent to glomerular inflammation.

The arteriolar changes in the case reported here were limited to a large extent to the kidney. While there were a few evidences of arteriolar damage in the liver, the arterioles of the spleen, heart muscle and skeletal muscle appeared normal. No dilatation of the afferent glomerular arterioles could be found, and no hyaline necroses were present. The renal arterioles presented two definite and different forms of disease. First, there was intimal thickening with profound fatty degeneration in connection with an atrophic media, the condition that may be called arteriosclerosis. Secondly, in some arterioles, there was a medial hypertrophy and the intima was thickened from connective tissue proliferation, fatty changes being absent. This endarteritis obliterans was also found associated with medial atrophy in some of the smaller arteries and arterioles. Arteriolar damage in the skeletal muscles was looked for carefully, and none was found. It was evident in this case that the disease of the smaller arteries and arterioles was not widespread as was found by Keith [22] in cases of malignant hypertension, but was limited entirely to the kidney. Occasionally, the media was found increased when the intima was intact.

SUMMARY

1. The clinical features of a patient, aged 12 years, with chronic glomerulonephritis and lipoid changes in the various organs, are described from the onset of the disease until death five years later. During the course of the disease it is seen that the symptoms were evanescent and varied so much from time to time that the proper interpretation of the clinical picture was difficult in some stages of the disease.

2. Lipoid deposits in the various parenchymatous organs are described, and their relationship to hypercholesterolemia is discussed. The atherosclerosis of the aorta and mitral valve is described and its dependence on hypercholesterolemia is pointed out.

22. Keith, Norman M.; Wagener, Henry P., and Kernohan, James W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141 (Feb.) 1928.

3. A description is given of the changes found in the arteries and arterioles of the kidney and other parenchymatous organs as well as those found in the skeletal muscles. The damage found in the renal arterioles is especially dwelt on.

The paintings and photographs that illustrate this paper were done by Mr. Leo Carl Massopust, artist at Marquette University School of Medicine.

HEMOCHROMATOSIS

REPORT OF A CASE, WITH STUDIES OF THE COPPER CONTENT OF THE LIVER *

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In 1889, von Recklinghausen described a form of pigmentation affecting many organs of the body which he called hemochromatosis. This condition is often accompanied in its terminal stages by diabetes—the bronze diabetes of French writers. While the number of recorded cases (approximately a few over 100) would indicate that the condition is rare, various observers have pointed out that it may easily be overlooked clinically in the early stages when the skin pigmentation, glycosuria and the hemosiderin granules in the urine are absent. Mills [1] reported that in seventeen pathologically advanced cases, only two were recognized during life and proved positive by the demonstration of hemosiderin in an excised piece of skin. Many patients, no doubt, die of intercurrent diseases before the positive clinical picture of hemochromatosis is established. Excellent pathologic and clinical studies are recorded in the literature. The characteristic pathologic picture is the presence of hemofuscin and hemosiderin in the cirrhotic liver, the pancreas, their regional lymph nodes and various other organs and tissues. Blanton and Healy,[2] in an analysis of fifty-three cases, noted that clinically the liver was found to be enlarged in most instances, markedly in 4 per cent, moderately in 10 per cent, slightly in 60 per cent, and not enlarged in 20 per cent. At necropsy, 95 per cent were recorded as enlarged. Ascites occurred in about one third of the cases. Glycosuria was present in 85 per cent of the cases with a record of such a study (average sugar content, 5 per cent). The spleen was more often not enlarged than otherwise on clinical examination. Among

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1. Mills, E. S.: Hemochromatosis with Special Reference to Its Frequency and to Its Occurrence in Women, Arch. Int. Med. **34**:292 (Sept.) 1924.

2. Blanton, W. D., and Healy, W.: Hemochromatosis: Report of Four Cases, Arch. Int. Med. **27**:406 (April) 1921.

forty-eight patients 31 per cent had slightly, 4 per cent moderately, and 4 per cent considerably, enlarged spleens; in 61 per cent the spleen was not palpable. At necropsy the abdominal lymph glands, as a rule, are firm and show massive collections of iron pigment, giving a gross appearance varying from brown to a chocolate color. The skin pigmentation occurs in about half of the cases, but microscopic studies of the skin show a wide disparity between the clinical appearances and the postmortem observations.

REPORT OF CASE

History.—A white man, aged 44, a construction iron worker, was admitted to the Pennsylvania Hospital, Oct. 2, 1928, and died, Oct. 26, 1928. The chief complaints were discoloration of the skin, weakness, enlargement of the abdomen and "yellow" stools. The patient stated that he had always been in good health prior to the present illness, except for gonorrhea at the age of 16. For many years he had used alcohol excessively, but none during the six months prior to admission. He had used no drugs. The onset of the present illness was dated to August, 1927, when he noted a change in the color of the skin. He felt well, however, until January, 1928, when the abdomen began to enlarge and the stools became clay-colored. Attacks of diarrhea occurred about once a week. Since the onset a loss of 20 pounds (9 Kg.) in weight occurred, with an insidious weakness which became progressively worse until he was compelled to stop working about six weeks before admission.

Physical Examination.—On admission, the patient was fairly well nourished; the face presented a curious discoloration somewhat suggestive of argyria. The neck and arms were brownish and suggested pigmentation due to exposure to the sun. The skin of the covered parts was "bronzed." The sclerae were icteric. There was no generalized lymphadenopathy. The tongue was coated, the breath offensive and pyorrhea alveolaris marked. Examination of the lungs showed nothing abnormal. The heart was enlarged, the cardiac sounds were clearly heard, and a soft systolic murmur was heard at the apex. The abdomen was distended, especially in the upper part. The liver was distinctly enlarged and felt irregular, but was not tender and the liver border was located about 10 cm. below the costal margin in the right midclavicular line. The spleen was easily felt and apparently touched the left lobe of the liver. There was distinct flatness in the flanks suggesting moderate ascites. The external genitals, the rectal examination and the extremities showed nothing of note. The temperature was normal, the pulse rate was 90, and the blood pressure was 110 systolic, 68 diastolic.

Laboratory Studies.—A small section of skin removed from the inner side of the forearm showed histologically the iron pigmentation characteristic of hemochromatosis.

The urine gave a positive Rous test for hemosiderin but was otherwise normal.

Studies of the blood showed a moderate secondary anemia, a sugar content of 105 mg. per hundred cubic centimeters and a urea nitrogen content of 16 mg. per hundred cubic centimeters, negative Wassermann and Kahn reactions and an immediate direct van den Bergh reaction with 3 mg. of bilirubin (6 units) per hundred cubic centimeters of blood.

The stools were semisolid and clay-colored, and bile was absent.

According to the bromsulphalein test (2 mg. per kilogram of body weight), there was impairment of liver function as 22 per cent of the dye remained in the blood after thirty minutes.

The fractional gastric analysis showed hypo-acidity, and biliary drainage revealed a greenish yellow bile which on culture was found to be sterile.

Clinical Course.—Temporary improvement in strength occurred during the first two weeks after admission, then cough, fever, dyspnea, cyanosis, increasing distention of the abdomen, increasing jaundice and progressive weakness rapidly followed each other and coma and death occurred. The last examination revealed the signs of pneumonia, increased fluid in the abdomen, and a terminal phlebitis and cellulitis of the right leg. The blood culture at the time showed a pure growth of the colon bacillus.

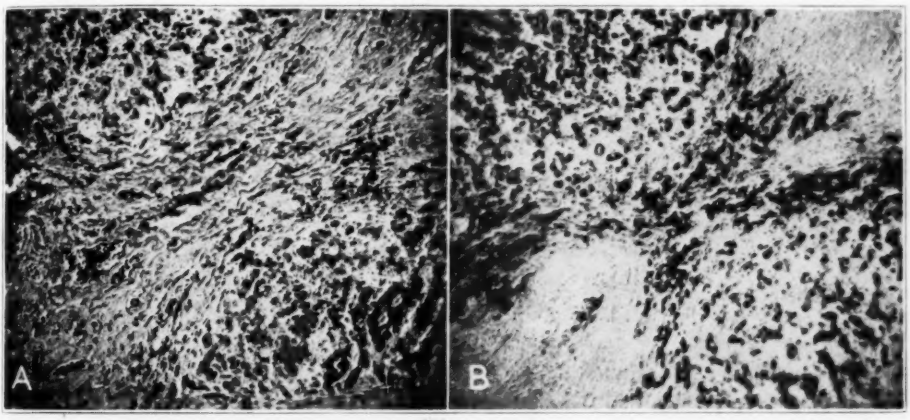

Fig. 1.—*A*, low power magnification of liver showing fibrosis and proliferation of bile ducts. Hematoxylin-eosin stain. *B*, same area stained for iron showing massive deposits in parenchymatous cells, especially those bordering the area of fibrosis.

Necropsy Studies.—The necropsy observations are in agreement with the excellent descriptions of Abbott, Opie, Sprunt, Mallory and others. Briefly, they are as follows:

The general appearance has been described. Permission could not be obtained for examination of the brain and spinal cord. The only macroscopic lesion in the thoracic cavity was bronchopneumonia. The liver, spleen and pancreas and their regional lymph nodes were enlarged and firm. There was approximately 1 liter of straw-colored, serous fluid in the peritoneal cavity.

The liver weighed 2,370 Gm. The surface was irregular but not nodular as in atrophic cirrhosis. On section, the cut surface was ochre-colored, with countless plainly visible interlacing bands of fibrous tissue. The pancreas was a dirty yellow and was markedly fibrosed. Both organs contained irregularly distributed, numerous, fine, dark green streaks.

The spleen weighed 670 Gm. It was dark red and firm with moderate prominence of the vessels and trabeculae. The capsule was thickened and opaque.

The mesenteric lymph nodes draining the liver, spleen and pancreas were dark brown, in contrast to the smaller, pale, edematous lymph nodes in the lower part of the abdomen.

No gross lesions of interest were found in the suprarenals, kidneys, bladder or elsewhere.

Microscopically, large deposits of hemofuscin and hemosiderin were found in the liver, pancreas, splenic capsule and their regional lymph nodes. Lesser deposits were found in the splenic parenchyma, suprarenals, heart and skin. Traces were found in almost any section of any organ. There was a tendency for the pigment to lie within the parenchymatous cells. Thus, in the liver (fig. 1), the Kupffer and liver cells contained practically all the deposits; in the pancreas (fig. 2), the acinar cells and the cells of the islands of Langerhans; in the heart, the muscle fibers; in the suprarenals (fig. 3), the cells of the zona glomerulosa,

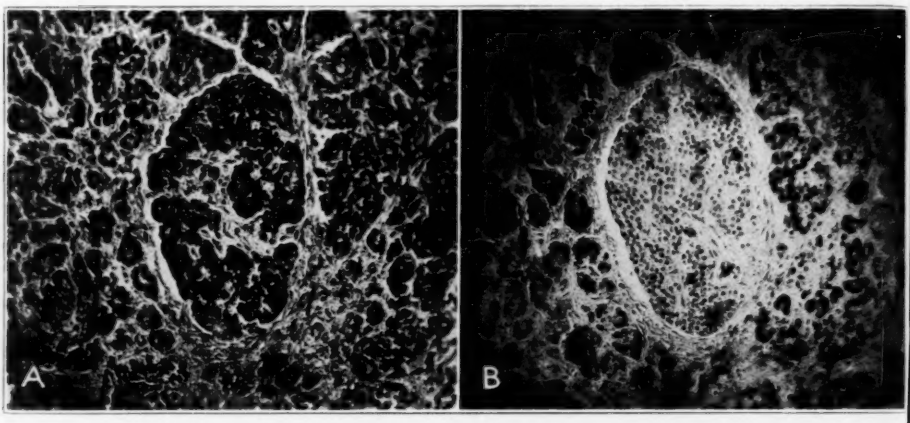

Fig. 2.—*A*, high power magnification of pancreas showing island of Langerhans and surrounding acini infiltrated with fibrous tissue. Hematoxylin-eosin stain. *B*, same areas stained for iron showing deposits in the acinar cells and to a less degree in the islet cells.

and in the lungs, the epithelial cells of the mucous glands of the bronchi. Minute deposits only were found in fibrous tissue. Traces were seen in some of the cells of the tubular epithelium in the kidneys and in the stroma of the tunica propria of the intestines.

In addition to the iron pigment, another pigment which we believe is melanin was found in the skin.

Chemical Studies.—Analyses of the tissues for copper were made by the method reported by Rose and Bodansky.[3]

The tissue was ground, treated with sulphuric acid, charred, treated with nitric acid and then ashed. The ash was extracted with hydrochloric acid and

3. Rose, C., and Bodansky, M.: Biochemical Studies on Marine Organisms, J. Biol. Chem. **44**:99, 1920.

the iron removed with hydrogen sulphide, after which the copper was estimated colorimetrically. Our percentage of error was determined to be between 5 and 6 per cent, approximately the same as that found by Rose and Bodansky.

We found 140 mg. of copper per kilogram of fresh liver tissue and estimated the total copper content of the liver to be 331.8 mg.

In the spleen, there was less than 0.1 mg. per hundred grams of tissue, and therefore less than 1 mg. in the entire spleen.

As controls, two livers without pigment cirrhosis were analyzed. One contained less than 1 mg. of copper per kilogram of tissue and the other 9 mg. of copper per kilogram of fresh tissue.

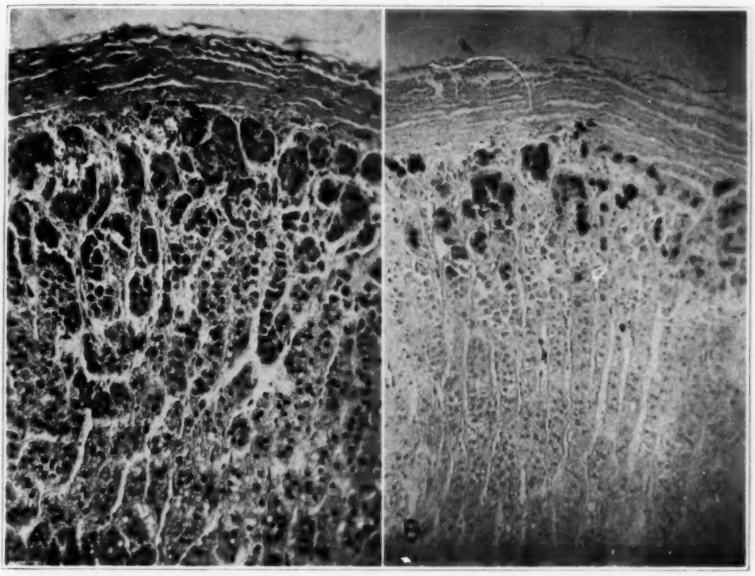

Fig. 3.—*A*, high power magnification of suprarenal gland, showing increased pigmentation in zona glomerulosa of the cortex due, as indicated by *B*, to iron pigment.

The estimate of the iron content was probably inaccurate, as the liver had been kept in Klotz's solution for several weeks before analysis. We used Kennedy's[4] method of digesting the organic matter in a mixture of perchloric and sulphuric acids, then treating it with a solution of sodium sulphocyanate and extracting the resulting ferric salt with amyl alcohol. This alcoholic solution was compared in a colorimeter with a standard iron solution.

The iron content of the liver was estimated to be 6.2 Gm. per kilogram of tissue, the entire liver, on this basis, containing 14.7 Gm. of iron.

The results of analyses of human organs for copper and some of the figures for iron are shown in tables 1 and 2.

4. Kennedy, R. P.: The Quantitative Determination of Iron in Tissues, J. Biol. Chem. **74**:385, 1927.

COMMENT

The cause of the excessive deposition of iron is not known. In the past few years, Mallory [5] has suggested that copper may be the primary etiologic factor in hemochromatosis. He divided nineteen patients into three groups: (1) those giving an alcoholic history, seven cases; (2) those who had occupational exposure to copper, four cases; (3) those whose histories throw no light on a possible cause, eight cases. Mallory regarded the chief action of copper absorbed in the body as hemolysis of the red blood cells with the liberation of hemoglobin in the circulation. Part of this is eliminated, but any excess is deposited in a

TABLE 1.—*The Copper Content of the Liver and Other Organs in Cases Not Showing Hemochromatosis*

	Organs Examined	Number of Cases	Milligrams of Copper per Kilogram of Tissue	Grams of Iron in Entire Liver	Comment
Flinn and Von Glahn	Livers	20	2.30-12.42	...	
	Livers	2	3.74	...	Copper workers
			5.34	...	
Mallory	Livers	4	0.78-20.40	...	
Pennsylvania Hospital	Livers	2	1.00 and 9.00	...	
Wells	Livers	Normal	.....	0.3	

TABLE 2.—*The Copper Content of the Liver and Other Organs in Cases Showing Hemochromatosis*

	Organs Examined	Number of Cases	Milligrams of Copper per Kilogram of Tissue	Grams of Iron in Entire Liver
Mallory	Liver	1	1.48	.....
	Bone	1	3.12	.....
	Liver and other organs	2	3.52 and 3.56	.....
	Liver and kidney	1	19.14	.....
Pennsylvania Hospital	Spleen	1	Trace	.....
	Liver	1	140.00	14.7(?)

changed condition as hemofuscin in the liver and other organs. In many kinds of cells, this is broken down with formation of hemosiderin, the whole process leading to necrosis and later sclerosis. Mallory showed experimentally that copper powder is absorbed through the respiratory or gastro-intestinal tracts and that there follows a deposition of yellow pigment, hemofuscin, in the liver, heart, kidneys, bone marrow and probably in other organs. He noted that citric and other acids, so frequently present in foods, are efficient solvents for copper. Copper

5. Mallory, F. B.; Parker, F., and Nye, R. N.: Experimental Pigment Cirrhosis Due to Copper and Its Relation to Hemochromatosis, J. M. Research **42**: 461, 1921. Mallory, F. B.: The Relation of Chronic Poisoning with Copper to Hemochromatosis, Am. J. Path. **1**:117, 1925; Hemochromatosis and Chronic Poisoning with Copper, Arch. Int. Med. **37**:336 (March) 1926.

cooking vessels, water pipes, cocktail shakers, "moonshine" whisky, copper dust in certain occupations, and a number of other possible sources of copper cause every one to be exposed to ingestion of the metal.

More recently, Lindow, Elvehjem and Peterson [6] determined the copper content of about 160 samples of the common food material. The figures range from 0.1 mg. of copper per kilogram of fresh celery to 44.1 mg. per kilogram of fresh calf liver. The degree of variation in the copper content of foods falling in the same class was less than that of either manganese or iron. A wide distribution of copper in food materials was found, no food examined being without this element.

A small quantity of copper is considered as a normal constituent of various organs and body fluids by McHargue [7] and by Warburg and Krebs.[8] The latter found approximately 0.0017 mg. of copper per cubic centimeter of blood and about the same amount associated with the serum proteins. McHargue, analyzing the organs of cattle, found that the liver was the richest in copper; and in this organ the highest amounts were found in early life. The liver of a calf born dead contained 908 mg. of copper per kilogram of dried material, of a calf 5 days old 400 mg. of copper, and of an ox 50 mg. The spleen of the ox contained 16.6 mg. and lean meat 4 mg. per kilogram of dried material.

Supplee and Bellis [9] and also Quam and Hellwig [10] found that the copper content of milk varied from 0.2 to 0.8 mg. per liter. The amounts were quite constant over four states and without any apparent correlation between diet and the quantity of copper present.

We do not know the effect of feeding copper-free diets over long periods, but we can state that all human beings and many, if not all, other animals ingest copper in varying amounts with each meal.

Hall and Butt [11] have obtained experimental results which support the observation that copper salts ingested over long periods of time produce in rabbits a pigment cirrhosis closely resembling the early manifestations of hemochromatosis in man. However, they have shown that alcohol not only fails to hasten or augment the production of pigment

6. Lindow, C. U.; Elvehjem, C. A., and Peterson, W. H.: The Copper Content of Plant and Animal Foods, J. Biol. Chem. **82**:465 (May) 1929.

7. McHargue, J. S.: The Association of Copper with Substances Containing the Fat-Soluble A Vitamin, Am. J. Physiol. **72**:583, 1925.

8. Warburg, O., and Krebs, H. A.: Loosely Bound Copper and Iron in Blood Serum, Biochem. Ztschr. **190**:143, 1927.

9. Supplee, G. C., and Bellis, B.: J. Dairy Sc. **5**:455, 1922.

10. Quam, G. N., and Hellwig, A.: The Copper Content of Milk, J. Biol. Chem. **78**:681, 1928.

11. Hall, E. M., and Butt, E. M.: Experimental Pigment Cirrhosis Due to Copper Poisoning, Arch. Path. **6**:1 (July) 1928.

cirrhosis, but reduces materially the storage of copper in the liver in both rabbits and white rats. They did not accept a factor of increased blood destruction. Hall and Butt, Dunn,[12] Howard and Stevens [13] and others have submitted evidence that increased hemolysis does not account for the pigment. The chief reasons are: (1) Anemia does not necessarily exist; (2) no tests for hemolysis are positive; (3) there are no signs of activity in the bone marrow and other hematopoietic organs; (4) there is a slow but definite retention of food iron; (5) the distribution of iron in hemochromatosis and in the hemolytic anemias is quite distinct. In hemochromatosis the spleen and bone marrow are pigmented to a slight degree as compared to the liver, pancreas and some other organs. In the hemolytic anemias, the reverse is true. As Rous and Oliver [14] have shown in their experiments with blood transfusions over long periods, the spleen and bone marrow collect hemosiderin to the limit of their capacity, after which the liver begins to be pigmented. Thus, it is unlikely that copper causes hemolysis with a resulting storage of iron.

Some recent studies indicate that copper may play an important part in the normal metabolism of iron. Hart, Steenbock, Waddell and Elvehjem [15] discovered during the course of experimental investigations of the rôle of iron in nutrition that copper may be a factor in the building of hemoglobin in a mammal. Experimentally, in the treatment for anemia in rats they found that liver extract was just as effective as it has been found to be in man, and that this effectiveness could be duplicated by the use of copper alone which is a constituent of the Lilly liver extract which they used. They did not know how copper in the presence of iron and an otherwise satisfactory diet functions in hemoglobin building, especially since copper is not a constituent of hemoglobin. They suggested that copper may act as a catalyzer for some reactions concerned in hemoglobin building just as iron functions in the production of the noniron-containing chlorophyl molecule.

Flinn and Von Glahn [16] conclude from careful feeding experiments on animals with and without the addition of copper to the dietary that:

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12. Dunn, J. S.: Hemochromatosis, Lancet **2**:334, 1921; Brit. M. J. **2**:783 (Nov. 12) 1921.

13. Howard, C. P., and Stevens, F. A.: The Iron Metabolism of Hemochromatosis, Arch. Int. Med. **20**:896 (Dec.) 1917.

14. Rous, P., and Oliver, J.: Experimental Hemochromatosis, J. Exper. Med. **28**:629, 1918.

15. Hart, E. B.; Steenbock, H.; Waddell, J., and Elvehjem, C. A.: Copper as a Supplement to Iron in Hemoglobin Building in the Rat, J. Biol. Chem. **77**: 797, 1928.

16. Flinn, F. B., and Von Glahn, W. C.: A Chemical and Pathological Study of the Effects of Copper on the Liver, J. Exper. Med. **1**:5, 1929.

"It is apparent that copper is not the cause of the pigment deposits in the liver of the rabbit, since the same change is produced when sodium acetate is given with the standard diet. Furthermore, when rabbits are fed on a diet of carrots exclusively, the deposition of pigment occurs with greater rapidity than with copper or its compounds and the standard diet. The changes resulting in the livers of the carrot-fed animals are identical in every way with those seen following large doses of copper and in animals given comparable doses of sodium acetate." Thus, that which only copper and possibly zinc were supposed to accomplish in pigmentation of the liver is found to occur with the use of sodium acetate or of carrots. How many other combinations can do the same is a matter of pure conjecture.

In hemochromatosis there is a tremendous increase in the quantity of iron in the body, especially in the liver. It seems that there is also an increase in copper. As food iron is retained, might not copper be retained, and zinc, manganese and other substances? We have found no reference to analyses for elements other than iron and copper, although complete analyses including those of zinc, manganese, nickel and bismuth might result in interesting and enlightening data.

CONCLUSIONS

1. A case of hemochromatosis without diabetes is reported.

2. The copper content of the liver was found to be 140 mg. per kilogram of fresh tissue, or 331.8 mg. for the entire organ.

3. The copper content of the spleen was found to be less than 1 mg. for the entire organ.

4. The estimated quantity of iron in the liver is probably inaccurate but was found to be at least 6.2 Gm. per kilogram of tissue or 14.7 Gm. for the entire organ.

5. No analyses were made for zinc, manganese, nickel or other heavy metals.

6. It is unlikely that increased hemolysis is the cause of the iron pigmentation.

7. It is likely that the rôle played by copper is secondary to an unknown etiologic agent.

A COMPARISON OF THE BLOOD SUPPLY OF THE RIGHT AND LEFT VENTRICLES IN CHILDHOOD*

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The differences in the blood supply of the right and left ventricles have not been sufficiently emphasized. The reason for this probably lies in the fact that most of the recent contributions to the knowledge concerning the coronary circulation have been acquired from a study of cleared specimens of the heart. These preparations are seldom entirely transparent. Consequently, in the thicker portions, such as the left ventricle, the arterial tree is incompletely shown. The roentgen method also has been used by many observers. This method is likely to give misleading pictures, owing to the fact that the interventricular septum is crescent-shaped, which makes it difficult to distinguish the vessels of the septum from those of the cardiac wall.

On the contrary, specimens prepared by the celluloid corrosion method are better suited for a comparison of the blood supply of the two ventricles. If casts of the cavities of the heart, as well as of the coronary arteries, are made according to the technic that I [1] described recently, the relation of the vessels is fairly well maintained. In the present work care was taken to inject celluloid mass (celluloid and camphor dissolved in acetone) of equal strength (with contrast colors) into the two coronary arteries simultaneously and at the same pressure. At the same time, a thicker celluloid mass was injected into the cardiac cavities in order to make a cast of the interior of the heart. When the mass hardened, the muscle tissue was removed by corrosion in hydrochloric acid and subsequent washing in water.

For the demonstration of the blood supply of the interventricular septum, as shown in figure 1, only slight variation in the technic is necessary. A heart in which the foramen ovale is closed must be selected. Either side of the septum may be demonstrated if water is

* Submitted for publication, July 12, 1929.

* From the Section on Pathologic Anatomy, the Mayo Clinic.

* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, June, 1929.

1. Whitten, M. B.: A Review of the Technical Methods of Demonstrating the Circulation of the Heart: A Modification of the Celluloid and Corrosion Technic, Arch. Int. Med. **42**:846 (Dec.) 1928.

injected into that side of the heart, and the celluloid mass, in the usual manner, into the opposite auricle and ventricle. A cast is thus made of only one side of the heart, whereas the opposite side is distended at the same pressure to prevent distortion. The remainder of the technic is the same as that employed in making casts of the entire heart.

Fig. 1.—Cast of the left auricle and ventricle. The interventricular septum is seen from the right side. Many deep branches leave the anterior descending branch of the left coronary artery, at right angles, to supply the interventricular septum. The course of the anterior descending artery around the apex is shown, as well as the portion of the interventricular septum supplied by each coronary artery. *A* indicates the anterior descending artery (left coronary artery); *P*, the posterior descending artery (right coronary artery).

In the celluloid casts of the heart, since the myocardial tissue has been removed entirely, the deeper blood vessels are clearly seen even in the thicker left ventricle. The celluloid cast of the interior of the

heart shows the size, shape and contour of the chambers, forms a support for the blood vessels and depicts relationships even after all the tissues of the living heart have been corroded away. Celluloid injected into the arteries penetrates to the capillaries, but not through them; for this reason, the resulting cast accurately portrays the arterial tree uncomplicated by venous branches. Smaller vessels may be removed for microscopic study. All the structures are shown in three dimensions; hence, there is not the confusion in their interpretation that often occurs in the case of roentgenograms or even stereoroentgenograms.

THE RELATIVE VASCULARITY OF THE TWO VENTRICLES

Gross [2] is the only one who has given any detailed account of the changes occurring in the relative vascularity of the right and left ventricles from birth, throughout life, to old age. A few men, such as Bizot,[3] Valentin [4] and Müller, have measured the relative thickness, weight or circumference of the two ventricles. Bizot's determinations (1837) are far from accurate. His measurements showed the left ventricle to be from 2.6 to 4.8 times as thick as the right, but did not show any variation that might suggest a difference in the relative thickness of the two ventricles at various ages. His only comparison of the circulation of the two ventricles was the observation that as a general rule the orifice of the left coronary artery was larger than that of the right, early as well as later in life. Valentin compared the thickness, weight and volume of the walls of the two ventricles. Regardless of the sex of the animal studied, he found that the ratio of the right ventricle to the left was always close to 1 : 2, no matter what measurements were compared.

According to Tandler,[5] Beneke (1879) measured volumetrically the relative mass of the right and left ventricles. Beneke found the relationship of the mass (by volume) of the right ventricle to that of the left, in man, to be 1 : 2.26 between the ages of 17 and 25 years and 1 : 2.02 between the ages of 27 and 73 years. His figures indicate that there is no increase in the preponderance of muscle mass of the left ventricle, as compared with the right, after the period of 17 to 25 years of age. In fact, his data suggest decrease in the predominance of the left ventricle for the period between 27 and 73 years.

2. Gross, Louis: The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, Paul B. Hoeber, 1921.

3. Bizot, J.: Recherches sur le couer et le Système Artériel chez l'Homme, Mém. Soc. méd. d'obst. **1**:262, 1837.

4. Valentin, G.: Ueber die Gegenseitigen Massenverhältnisse der Rechten und der Linken Kammer des Herzens, Ztschr. f. rat. Med. **3**:317, 1844.

5. Tandler, Julius: Anatomie des Herzens, in von Bardeleben, Karl: Handbuch der Anatomie des Menschen, Jena, Gustav Fischer, ed. 3, pt. 1, 1913.

Müller's work (1883) on the relative weights of the right and left ventricles has been reviewed by Tandler. A portion of one of Müller's tables is given in the accompanying table, the second and third columns of which give Müller's figures for the average weights of the right and left ventricles at various ages. In the column at the extreme right, the ratio of the weight of the left ventricle to that of the right is shown. Although there is considerable variation, the predominance of the weight of the left ventricle, as compared with the right, increases from a ratio of 1.2:1 at 1 week of age up to 2:1 at 7 to 12 months of age. From the age of 12 months on there is considerable variation, but as a whole the ratio between the weights of the two ventricles remains

TABLE 1.—*Weight of the Right and Left Ventricles at Various Ages According to Müller and as Presented by Tandler* *

Age	Right Ventricle (Including Septal Wall), Gm.	Left Ventricle (Including Septal Wall), Gm.	Ratio of Weight of Left Ventricle to That of Right Ventricle†
1 week	6.14	7.45	1.213
2 weeks	5.34	7.65	1.433
3 weeks	5.39	7.93	1.471
4 weeks	5.41	8.83	1.632
2 months	4.28	7.28	1.701
3 months	5.47	9.98	1.825
4 to 6 months	6.55	12.35	1.886
7 to 12 months	8.04	16.31	2.029
2 years	12.42	22.00	1.771
3 years	14.98	32.15	2.146
4 to 5 years	16.24	34.20	2.106
6 to 10 years	25.01	50.97	2.038
11 to 15 years	34.00	67.10	1.974
16 to 20 years	63.40	117.10	1.934
21 to 30 years	70.80	125.10	1.767
31 to 40 years	71.00	135.60	1.910
41 to 50 years	72.80	143.90	1.977
51 to 60 years	75.30	151.60	2.013
61 to 70 years	77.70	155.70	2.004
71 to 80 years	73.20	142.60	1.948
81 to 90 years	61.60	144.40	2.344

* This table represents the average weights of hearts of male human beings. The ratio between the weights of the two ventricles was essentially the same in females.

† I have calculated the relation of the weight of the left ventricle to that of the right from the results obtained by Müller and shown in the two preceding columns.

practically the same. Müller's results were interpreted by Gross as indicative of a constantly increasing preponderance of the weight of the left ventricle, as compared with the right, as age increased. The ratio of the weight of the left ventricle to that of the right, as calculated from Müller's data and recorded in the accompanying table, shows, however, that there is no consistent increase in the predominance of the left ventricle after the 7 to 12 month period of life has been reached.

Gross found that the right and left ventricles received about an equal blood supply at birth, and he believed that this ratio remained about the same until the second decade of life, when the left ventricle became a little more vascular than the right. In the third decade of life, Gross found the left ventricle to be definitely more vascular than the right, and he believed that there was an increasing pre-

dominance of the vascularity of the left ventricle as compared with the right throughout the succeeding decades of life. He explained that this was due, not so much to a definite loss in blood vessels on the right side, as to a relative loss as compared with the ever increasing vascularity of the left ventricle. In other words, he believed that the right ventricle lagged behind the left consistently and increasingly throughout life, as far as vascularity was concerned. Gross was inclined to believe that this loss of blood vessels, as compared with the left ventricle, produced an increasing decline and failure of the right side of the heart, and that this accounted for the frequency of deaths from pneumonia in elderly persons. He suggested that "a man is as old as his right coronary artery."

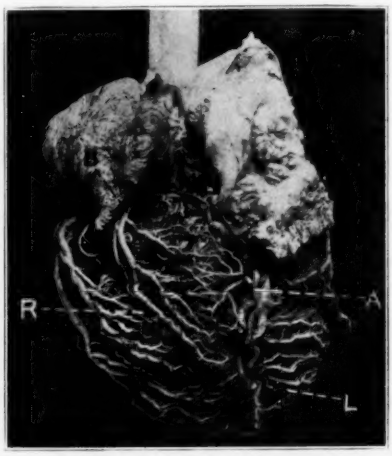

Fig. 2.—Anterior view of celluloid cast of heart of fetus at full term, showing equal vascularity of right and left ventricles. *R* indicates the right ventricle; *L*, the left ventricle; *A*, the anterior descending artery (left coronary artery); *B*, the right coronary artery.

Campbell[6] (1928), using stereoscopic roentgen technic, asserted that he verified the work of Gross concerning the comparative vascularity of the ventricles. He stated: "The alteration in the relative vascularity of the ventricles which comes with advancing age, and results in a decrease of the blood supply to the right heart through an increase in the development of anastomotic branches was also verified."

In the work to be reported in this paper, a comparison was made of the blood supply of the two ventricles. The hearts were prepared

6. Campbell, J. S.: Stereoscopic Radiography of the Coronary Circulation, Lancet **2**:168, 1928.

by the celluloid-corrosion method. The auricular circulation was excluded from this study because of its great variability and because it does not present a definite relationship to the ventricular circulation. The blood supply of the interventricular septum also has been excluded from the present study because of the difficulty of deciding what portion of the septum belongs to each ventricle.

Some time ago, my attention was called to the fact [7] that in a cast of the heart and injected coronary vessels of a child who died at 13½ months of age, the left ventricle was much more vascular than

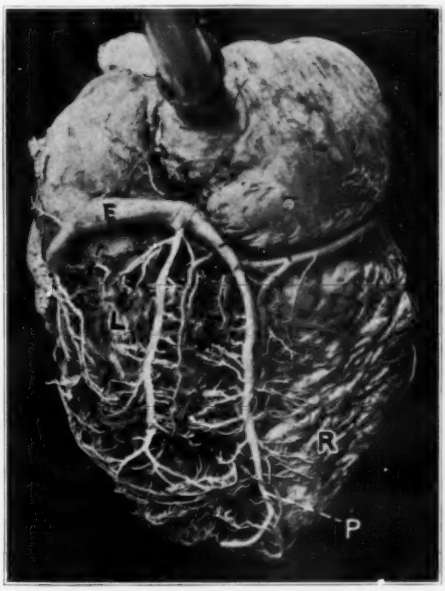

Fig. 3.—Posterior view of celluloid cast of heart of child aged 2 years, showing moderate vascular preponderance of the left ventricle. *R* indicates the right ventricle; *L*, the left ventricle; *P*, the posterior interventricular vein; *E*, the left coronary artery; *F*, the right coronary artery.

the corresponding right ventricle. This is contrary to the data of Gross. An anterior view (fig. 4) of this heart accompanied a previous paper.[1] As it is possible, however, that the two coronary arteries were not injected under exactly the same standard conditions in this preparation, care has been taken since to inject the two coronary arteries under the same standard conditions, and a number of hearts of chil-

7. Barnes, A. R.: Personal communication to the author.

dren of various ages have been studied in order to determine at what age the left ventricle becomes more vascular than the right. In order to compare the blood supply of the two ventricles, illustrations of celluloid casts are shown in figures 2 to 8. The blood vessels of a ventricle are fairly equally distributed, and the only reason for showing the posterior surface in most of the cases is that it presents a broad, flat surface which will show in a single photograph an equal portion of the two ventricles.

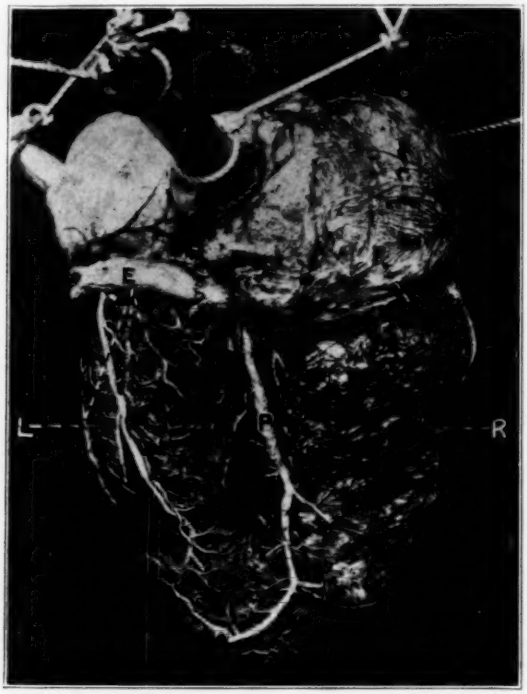

Fig. 4.—Posterior view of celluloid cast of heart from a child aged 6 years. The vascularity of the left ventricle predominates markedly over that of the right. *R* indicates the right ventricle; *L*, the left ventricle; *P*, the posterior interventricular vein; *E*, the left coronary artery; *F*, the right coronary artery.

STUDY OF HEARTS BY THE METHOD OF CORROSION

In the cast of the heart of a fetus of 6 months, the right and the left ventricles possess an approximately equal vascularity. In figure 2, an anterior view of the cast of the heart of a fetus at full term reveals equal vascularity of the two ventricles. At 2 years of age (fig. 3), the left ventricle is definitely more vascular than the right. This is not

so apparent in the base of the left ventricle, near the obtuse margin, for some of the branches of the left circumflex artery have been broken off. Elsewhere, however, the left ventricle has a more profuse blood supply than the right. In the fourth year of life, the left ventricle possesses rather marked vascular preponderance. At 6 years (fig. 4) the vascularity of the left ventricle has become still more marked than that of the right. This predominance is evident in spite of the fact that in the heart which was selected for study, a number of large

Fig. 5.—Anterior view of celluloid cast of heart of child, aged 10 years. The left ventricle is markedly more vascular than the right on the anterior as well as on the posterior surface of the heart. *R* indicates the right ventricle; *L*, the left ventricle; *A*, the anterior interventricular vein; *E*, the right coronary artery; *F*, the left coronary artery.

branches of the right coronary artery coursed transversely across the posterior surface of the right ventricle to supply the posterior portion of the interventricular septum. Usually these vessels arise from the deep surface of the posterior descending artery, as it follows down the posterior interventricular sulcus, and consequently, they are hidden from view and do not show on either ventricle. In the heart of the

child, aged 7 years, the left ventricle had a greater blood supply than the right, but the difference was not as marked as it was in the preceding cast.

In a previous paper [1] a posterior view (fig. 2) was presented of the cast of the heart of a child, aged 10 years. The vascularity of the left ventricle is extremely well developed and shows a marked predominance over the blood supply of the opposite ventricle. In fact,

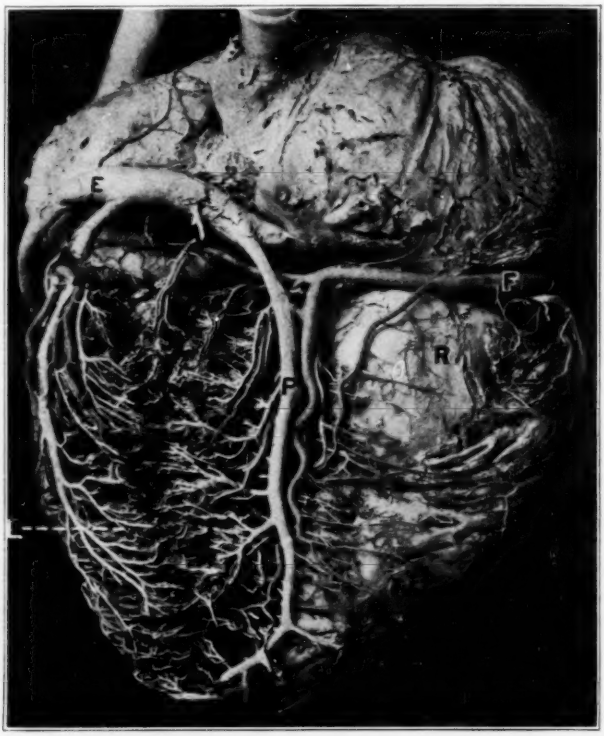

Fig. 6.—Posterior view of celluloid cast of heart from a child, aged 14 years. The left ventricle is markedly more vascular than the right. *R* indicates the right ventricle; *L*, the left ventricle; *P*, the posterior interventricular vein; *E*, the left coronary artery; *F*, the right coronary artery.

at 10 years of age, the vascular preponderance of the left ventricle appears to be as well developed as Gross found it to be one or two decades later. In order to demonstrate that the preponderance in vascularity of the left ventricle is not confined to the posterior surface of the heart, an anterior view of the same cast is shown in figure 5.

In the heart of the subject of 14 years of age (fig. 6), the vascular preponderance of the left ventricle is just as marked as it was at 10 years of age. The last two figures also show that the venous as well as the arterial circulation of the left ventricle predominates over that of the opposite ventricle.

As this study was begun to determine the age at which the left ventricle became better supplied with blood than the right, a special

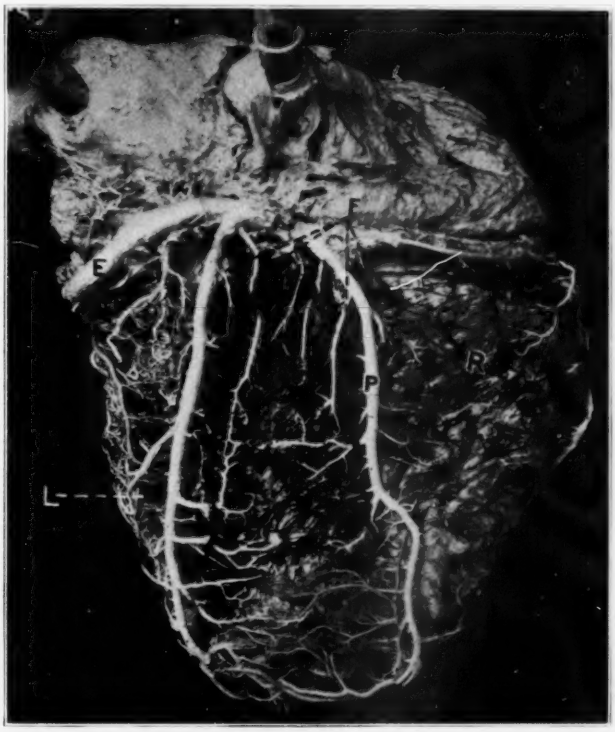

Fig. 7.—Posterior view of celluloid cast of heart from a woman, aged 28. The vascular preponderance of the left ventricle is evident. *R* indicates the right ventricle; *L*, the left ventricle; *P*, the posterior interventricular vein; *E*, the left coronary artery; *F*, the right coronary artery.

effort was made to secure a series of hearts of children. Since it is evident enough that the left ventricle is the more vascular in adult life, illustrations of only one cast of an adult heart are presented. This is from a patient who died at the age of 28 years (fig. 7). The left ventricle is definitely more vascular than the right.

All of the casts so far studied were made from normal hearts. In the cast illustrated in figure 8 the right ventricle is seen to be much

more vascular than that observed in the normal hearts of adults. This patient had a hypertrophied right ventricle and a corresponding increase in the blood supply of this portion of the heart.

COMMENT

The illustrations demonstrate that during the latter part of fetal life, and at birth, the right and the left ventricles are about equally vascular.

Fig. 8.—Celluloid cast of heart from a man, aged 71. There is increased vascularity of the hypertrophied right ventricle. *R* indicates the anterior surface of right ventricle; *E*, the branch of right coronary artery; *F*, the anterior descending branch of left coronary artery.

In fact, the blood supply of the two ventricles is so nearly equal that, unless one is familiar with the normal course of the vessels, one is likely to be at a loss to determine which is the right coronary artery and which the left.

It has been observed, also, that the left ventricle becomes more vascular than the right much earlier than the work of Gross would indicate.

Whereas he did not describe any difference in the vascularity of the two ventricles previous to the second decade of life, and did not find a marked difference in their relative vascularities until the third decade, the casts observed in this study indicate that the vascular preponderance of the left ventricle is well in evidence at the end of the second year of life, that by the sixth year it has become marked and that by the tenth year there is an enormous preponderance of blood vessels in the left ventricle. That this preponderance persists throughout life in normal hearts is indicated by the casts of adult hearts. The casts, therefore, demonstrate a preponderance that increases up to the tenth year of life, but which from that time on does not appear to increase with age but to continue at about the same ratio.

It has been shown also that there is an increasing venous preponderance in the left ventricle corresponding rather closely with that of the arteries.

The work of Müller (table) shows that during the first week of life the weight of the left ventricle is not much in excess of that of the right. If the weights of the two ventricles are studied with respect to the changes that occur with increasing age, it is found that the difference between them increases gradually but regularly until the age of 7 to 12 months. After this, there is no consistent increase in the preponderance of the left ventricle over the right with respect to weight. If Müller's work may be accepted as fairly accurate, it is evident from a study of the right hand column of the tabulation that there is no increasing predominance in the weight of the left ventricle throughout life; instead, after the age of 7 to 12 months there remains an almost constant ratio between the weights of the two ventricles. Beneke's work also indicates that there is no increasing preponderance of the weight of the left ventricle over that of the right after the ages of 17 to 25 years. Consequently, I cannot agree with Gross that Müller's work is indicative of a constantly increasing preponderance in the weight of the left ventricle.

In the heart at birth there usually cannot be demonstrated any difference in the thickness of the two ventricles. I have shown that at this time the two ventricles are equally well supplied with blood. In all of the remaining normal hearts studied, that is, from the age of 2 years on, the left ventricle was definitely thicker than the right. In these hearts, there was found to be a left-sided vascular preponderance in every case, and at the tenth year it was concluded that the predominance of the blood vessels in the left ventricle was so marked that an increasing preponderance could not be demonstrated thereafter.

The observations indicate that the vascularity in some degree is in relation to the weight and thickness of the ventricle. If Müller's

results are accepted, it would seem that the muscle weight reaches its constant ventricular ratio at an earlier age than the blood supply. Additional proof that there is some relationship between the thickness and the weight of the ventricle, and the blood supply, is evidenced by the increased vascularity that appeared in an hypertrophied right ventricle (fig. 8). Comparison of the blood vessels in the right ventricle, in this case, with those of the normal hearts, seen in the previous figures, will show this marked increase in circulation.

SUMMARY AND CONCLUSIONS

1. A method of demonstrating the circulation of the interventricular and interauricular septums by a modification of the celluloid corrosion technic has been described.

2. At birth and during the latter part of fetal life, the right and left ventricles are about equal in vascularity.

3. By the end of the second year, the left ventricle has become definitely more vascular than the right. This preponderance increases until about the tenth year of life, after which no increase in the vascular preponderance of the left ventricle could be demonstrated.

4. There is a definite preponderance of the venous circulation in the left ventricle as compared with that of the right.

5. It is suggested that there is some relationship between the thickness of the ventricular wall and its blood supply in the absence of marked arteriosclerosis.

COMPLETE HEART BLOCK

ROENTGEN-KYMOGRAPHIC STUDY *

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This report is based on a study of two cases of complete heart block of many years' duration. The patients were unaware of the cardiac abnormality and suffered no discomfort or limitation of activity therefrom. While such cases of compensated, complete, auriculoventricular dissociation are not so rare as to warrant the report of additional ones, there are some aspects of this type of case which are worthy of further study.

UNUSUAL FEATURES IN COMPLETE HEART BLOCK

Some of the unusual features encountered are: (1) absence of symptoms of inadequate circulation, including Stokes-Adams' attacks; (2) increased size of the heart; (3) high systolic and normal, or low, diastolic blood pressures, and (4) variations in the pulse force or volume.

Absence of Inadequate Circulation.—The clinical details of the two cases studied with the roentgen-kymograph have been reported elsewhere.[1] One case was that of a woman, aged 47, in whom complete heart block had existed, in all probability, since an attack of diphtheria in childhood. The other was that of a man, aged 77, in whom heart block was of indefinite duration, but probably of ten or more years, and most likely arteriosclerotic in origin. In each case the block was discovered incidentally, as neither patient suffered from any circulatory insufficiency. It is this adequate compensation for a serious cardiac lesion which lends such interest to these cases, which show, as a rule, no evidence of cardiac damage other than complete auriculoventricular dissociation.

Regarding the unusual features of the cases mentioned, it is well known that Stokes-Adams' attacks cease to occur when an idioventricular rhythm above from 20 to 25 has become established.

Size of the Heart.—The second feature, supernormal size of the heart, is a necessary consequence of the increased stroke volume. The cardiothoracic indices in my two cases and in a similar one reported by Smith [2] were above 0.5. This enlargement of the cardiac shadow results

* Submitted for publication, July 21, 1929.

* From the Stanford University Medical School, Division of Medicine.

1. Read, J. Marion: A Clinical Interpretation of Pulse Pressure, Am. Heart J. **2**:541 (June) 1927.

2. Smith, S. C.: High Grade Heart Block; the Influence of Posture, Respiration and Exercise, J. A. M. A. **76**:17 (Jan. 1) 1921.

probably from two factors. One is muscle hypertrophy, but the greater cause is larger blood volume within the heart's chambers. The high systolic pressure would indicate ventricular hypertrophy, and there is some evidence of auricular hypertrophy in the high P wave (fig. 1). I am aware of no postmortem studies in this type of case which would assist in determining the amount of muscle hypertrophy.

Blood Pressure.—The third feature, normal diastolic and wide pulse pressure, I have commented on previously.[1] Musser,[3] in 1917, reported some observations on two cases of complete heart block in women, aged 60 and 65. They each had normal diastolic and high systolic pressures, although in one the systolic pressure fell 100 mm. during a brief return to normal rhythm. From a study of his two cases and a review of the literature on heart block from 1904 to 1916, Musser concluded "That this high pressure is dependent more on increased blood mass discharged by the left ventricle than on the associated cardiac hypertrophy and peripheral sclerosis."

Stroke Volume.—It seems but logical to assume that stroke volume will have to be doubled when the pulse rate is reduced to half the normal rate if an adequate minute volume is maintained, as it is in compensated cases like the two I have studied.

That this is actually the case was shown by Lundsgaard[4] in 1916, and more recently (1927) by Liljestrand and Zander,[5] who studied the blood flow in a young man, aged 20, with complete heart block since childhood, but who "is able to perform very heavy muscular work and practises athletics." Following extensive studies of this man, the Swedish investigators said, "There can thus be no doubt that in this subject the low pulse rate is completely compensated by the increased ventricular output per beat, resulting in a normal blood flow. In this case, however, this also holds true during muscular work."

In a personal communication, Dr. A. V. Bock of the Massachusetts General Hospital gave me the data on the blood flow in another such patient, but with a constant 3:1 block. The pertinent data are: A man (A. B. C.), aged 58, had a pulse rate of 26 per minute. The blood pressure was 215 systolic and 100 diastolic. The blood flow was 3.68 liters per minute, or an output of 141 cc. per systole, which is nearly

3. Musser, J. H.: Heart Block Associated with High Blood Pressure, Arch. Int. Med. **20**:127 (July) 1917.

4. Lundsgaard, C.: Untersuchungen über das Minuten-volumen des Herzens bei Menschen: III. Messungen an zwei Patienten mit totalen Herzblock, Deutsches Arch. f. klin. Med. **120**:46, 1916.

5. Liljestrand, G., and Zander, E.: Studies of the Work of the Heart During Rest and Muscular Activity in a Case of Uncomplicated Total Heart Block, Acta med. Scandinav. **66**:501, 1927.

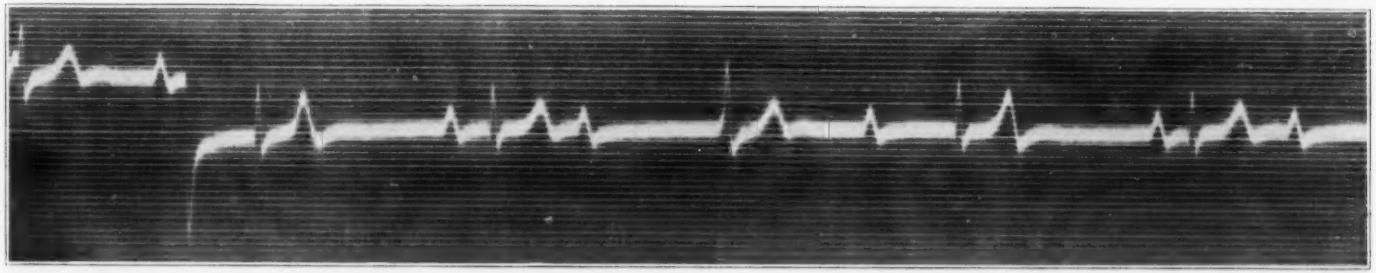

Fig. 1.—Second lead of the electrocardiogram in the case of a woman, aged 47. She had complete heart block since childhood. There were no manifestations of myocardial insufficiency. There is a high auricular wave in this and the other two leads.

double the average normal for a man weighing 146 pounds (66.2 Kg.). The interesting thing to note is the pulse pressure of 115 and the fact that there was compensation, for Dr. Bock wrote ". . . . he assured me that he had come into the hospital only at Dr. White's request to have himself checked up, and he denied symptoms of any kind. He appeared in excellent health and was able to indulge in vigorous exercise without dyspnea." He had been under observation for five years.

THE ARTERIOGRAM

To the palpating finger the pulse in compensated, complete heart block feels very full and strong and, because of the long diastole, seems

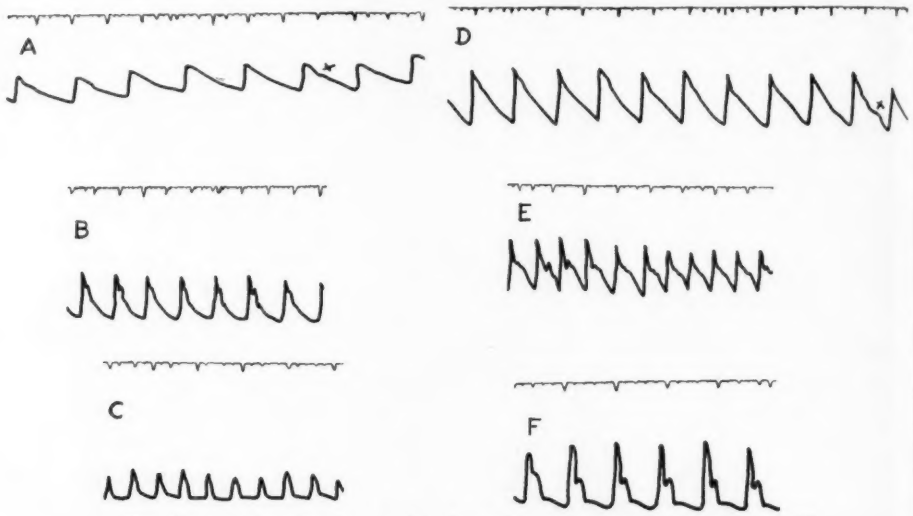

Fig. 2.—Arteriograms in complete heart block and aortic insufficiency with comparable blood pressures; these were retraced with india ink. In each of the heart block tracings is shown one of the notches which Mackenzie thinks are due to pressure on the base of the aorta from the contracting auricle. *A* (case 1), brachial arteriogram: blood pressure, 178 systolic and 82 diastolic; *B*, aortic insufficiency (syphilitic): blood pressure, 185 systolic and 42 diastolic; *C*, aortic insufficiency (syphilitic): blood pressure, 145 systolic and 45 diastolic; 178 systolic and 48 diastolic. *D* (case 2), brachial arteriogram: blood pressure, 170 systolic and 74 diastolic; *E*, aortic insufficiency (rheumatic): blood pressure, 116 systolic and 40 diastolic; *F*, aortic insufficiency: blood pressure, 135 systolic and 0 (?) diastolic.

to fall quickly. To ascertain the shape of the arterial wave and to compare it with arteriograms from cases of aortic insufficiency with approximately the same pulse pressure, I made several tracings, parts of which are shown in figure 2.

It is evident that the pulse wave in these cases more nearly resembles the normal, despite the deviation from normal pulse pressure, than it resembles the wave in aortic insufficiency with comparable blood pressures.

Because of the eccentricities of the polygraph, a comparison in height of the wave in patients with heart block and in normal subjects would be of little value. An interesting observation on this point was made by Musser [5] when one of his patients was so obliging as to revert to normal rhythm while an arteriogram was being made. Musser said:

> It is interesting to note the differences in size of the arteriogram waves where there is block and where the block has disappeared. The waves are almost twice as large when the rate is slow as compared with the heart beats when twice as rapid, demonstrating that where all other factors are equal, the adjustment levers being unchanged, a high pressure presumably causes large graphic arterial waves.

While it is inferred from the wide pulse pressure and height of the arterial wave that the stroke volume in compensated heart block is greatly increased, and this inference is borne out by experimental studies, there remains clinical confirmation by study of the heart itself.

THE ROENTGEN-KYMOGRAM

With a view to ascertaining several points which had arisen in a study of these cases of compensated, complete heart block, I undertook some investigations of the movement of the border of the heart. As roentgenograms of the heart in systole and diastole did not seem adequate or feasible, I resorted to the roentgen-kymograph as best suited to the purpose. This apparatus was first described in 1912 by Gott and Rosenthal,[6] and has since been used by Becker,[7] Crane [8] and Cohn and Stewart [9] in studying movements of the border of the heart.

Under the fluoroscopic screen the point of maximum ventricular movement was noted and its projection on the wall of the chest marked. The slit in the lead sheet was placed over this point and the roentgen-kymogram taken. It will be observed from figure 3 that in case 2 there is a marked difference between diastole and systole as denoted by the height and depth, respectively, of the waves. This is brought out by

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6. Gott, T., and Rosenthal, J.: Ueber ein Verfahren zur Darstellung der Herz-bewegunger mittelst Röntgenstrahlen (Roentgenkymographie), München. med. Wchnschr. **59**:2033, 1912.

7. Becker, T.: Die Analyse des Elektrokardrogrammes mittels der Röntgenkymographie, Deutsches Arch. f. klin. Med. **113**:216, 1914.

8. Crane, A. W.: Roentgenology of the Heart, Am. J. Roentgenol. **3**:513, 1916.

9. Cohn, G. E., and Stewart, H., Jr.: Evidence That Digitalis Influences Contraction of the Heart in Man, J. Clin. Investigation **1**:97, 1924.

comparison with a similar tracing from a normal male weighing 25 pounds (11.3 Kg.) more than the patient in case 2. Both roentgen-kymograms were taken under the same conditions, with the patients in a supine position, breath held, and at the same distance from target, etc. The tracings should be comparable, though I am aware of the criticism

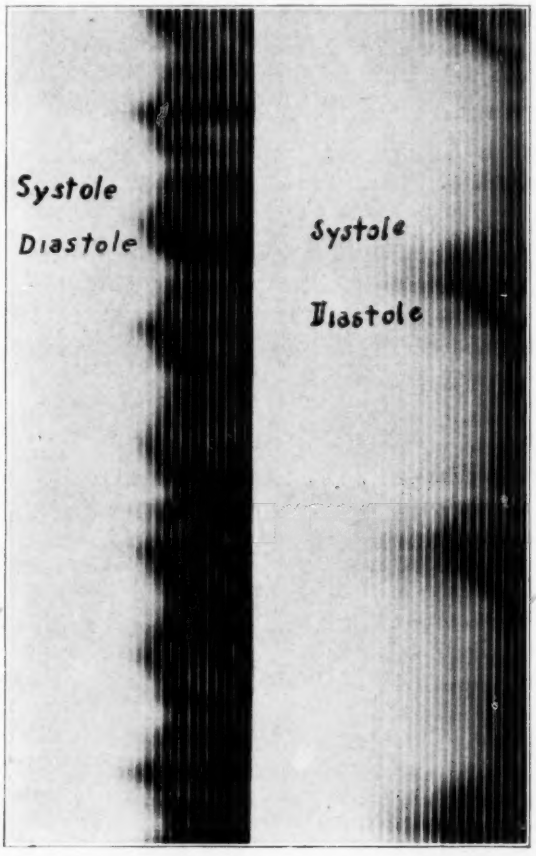

Fig. 3.—Roentgen-kymogram showing the curve produced by the point of maximum movement on the left ventricular border in a normal person and in a person with heart block, complete. The film moved past a 1 mm. slit in a lead shield, the slit being placed over the point of maximum movement as determined by fluoroscopic examination. The subject was prone; the speed of the film was about 4 cm. per second. Aside from the difference in heart rate, the chief point brought out by this comparison is the much greater amplitude of motion of the left ventricle in the case of heart block.

of this method of study by Stenström and Westermark.[10] They stated that the curves produced represent not only contraction of the border but traction and pushing from other parts of the heart. It seems most probable, however, that the marked differences in amplitude of ventricular movement seen in figure 3 are due to differences in systolic output and not to differences in traction or pushing since these should be approximately the same in each case.

It is recognized that movement at one point cannot be accepted as proof that the whole ventricle had as great an amplitude of motion, but great amplitude was confirmed by fluoroscopic examination and roentgen-kymograms taken at several points on the heart's border.

It becomes evident from the roentgen-kymogram that a patient with complete heart block, wide pulse pressure, high wave in the arteriogram and Corrigan-like pulse also has great amplitude of ventricular movement. By correlating these observations with the fact that such a patient is completely compensated with a pulse rate approximately one-half the normal, the clinician seems justified in attributing these phenomena to increased diastolic filling and the ejection of a supernormal volume of blood at ventricular systole.

EFFECT OF AURICULAR SYSTOLE

The obvious efficiency of the ventricle in compensated, complete heart block leads one to wonder about the effectiveness of auricular contractions in these patients. What is the relative importance of auricular contraction and venous pressure in filling the ventricle so completely?

The question has long been debated as to whether or not, even under normal conditions, auricular systole plays much part in filling the ventricle. Feil and Katz [11] studied the problem in a patient with alternating periods of auricular fibrillation and normal rhythm, using the duration of systolic ejection and total systole as criteria and concluded that their observations "give probable if indirect evidence of the dynamic importance of auricular systole in the normal heart beat of man."

I am not aware of any studies of the effectiveness of auricular systole on ventricular filling in complete heart block. But in seeking an explanation for the variations in the height of systolic pressure and variations in first sound intensity at the cardiac apex, I have come to the belief that these phenomena are due to different diastolic volumes expelled at systole. Variations in force of beat are present in auricular fibrillation and

10. Stenström, N. G., and Westermark, N.: A Study of the Activity of the Human Heart Simultaneously Recorded by X-Rays and Electrocardiogram, Acta radiol. **5**:408, 1926.

11. Feil, H. S., and Katz, L. N.: Evidence of the Dynamic Importance of Auricular Systole in Man, Proc. Soc. Exper. Biol. & Med. **20**:323, 1922-1923.

in the first normal beat following a ventricular premature systole, long diastolic periods preceding the large beat in each case. But in complete block in which the ventricular rhythm is regular, variations in the force of beat seem logically best explained by variations in the number of auricular contractions occurring during ventricular diastole, venous pressure being constant. I realize, however, that there is little support for this conception since the general belief, based on the work of Henderson, Straube and others, is that the auricular contraction plays little or no part in filling the ventricle.

But Gesell,[12] working with the heart-lung preparation, showed that "under the conditions of these experiments auricular systole increased ventricular output 50 per cent over that maintained by venous pressure alone." His results seem unequivocal and, since the problem is chiefly one of hydrodynamics, it does not seem unreasonable to assume that in human beings with complete heart block auricular systole plays a part in filling the ventricle. I am inclined to this view because it is the only explanation I can give of two phenomena observed in the clinical study of the two cases of heart block which inspired this report.

Variable Systolic Force.—The first of these phenomena is the variation in systolic pressure, already mentioned, which at times seemed to me like an alternation. That a variation in the height of the systolic pressure occurs with successive contractions I am certain from repeated sphygmomanometric studies, nor does this seem to be due to respiratory phases as it occurs in successive beats and not in cycles. Whether or not these variations result from variable volumes of blood ejected at successive beats, I cannot be sure. The roentgen-kymogram shows a variability in the size of successive systoles. Also the arteriograms show this, but because of the mechanical defects inherent in this method, I hesitate to stress this evidence strongly.

It is more difficult to show that variable volumes are present in the ventricle because different numbers of auricular contractions occurring during ventricular diastole have forced variable volumes into the ventricle. Such an explanation does not seem unreasonable from a study of the electrocardiogram in figure 1. The roentgen-kymograms (figs. 4 and 5) seem to show that the shape of the ventricular curve is influenced by the number and time of the auricular systoles occurring during ventricular diastole.

The other phenomenon was pointed out to me by the roentgenologist who made a fluoroscopic examination of one of these patients. During this examination a curious movement of the left ventricle was seen.

12. Gesell, R. A.: Cardiodynamics in Heart Block as Affected by Auricular Systole, Auricular Fibrillation, and Stimulation of the Vagus Nerve, Am. J. Physiol. **40**:367, 1916.

namely, relaxation seeming to occur in two stages; during the long diastole the ventricle would expand in the normal manner, but in a moment there would be a second enlargement of the ventricular shadow. This phenomenon was produced, I believe, by the normal early diastolic filling from venous pressure, possibly augmented by an auricular contraction, and, later in diastole another auricular contraction added to the volume of blood already in the ventricle and produced the second distention of the ventricle observed under the fluoroscope.

This patient's electrocardiogram shows usually an auriculoventricular ratio of about 2: 1, and during the greater number of ventricular diastolic periods two auricular systoles occur. In a continuous electro-

Fig. 4.—Roentgen-kymogram taken with two slits; one over the point of maximum movement of the left ventricle and long enough to include the right auricular border. The other slit, 4 cm. above the first, shows the movement of the aorta and vena cava. The film moved 1 cm. per second. The auricular systoles are marked by dots. Four ventricular and six auricular systoles are shown. The first, third and fifth auricular systoles occur close to the time of ventricular systole and produce larger waves in the vena cava. The shape of the ventricular curve is not constant, the second one having a more acute corner (the first part of diastole) produced, it seems, by an auricular systole occurring early in diastole. A small tip on the third ventricular curve may be due to auricular systole late in ventricular diastole.

cardiographic tracing 9½ feet long there were sixty-five heart cycles, and of this total two P waves fell in the diastolic period forty-two times.

The roentgen-kymogram in this case shows that diastole is not a perfectly smooth curve (fig. 5) and also that there is a variation in the extent of diastolic filling amounting to 50 per cent in some instances.

There have been two other phenomena observed in cases of complete heart block and several theories offered in explanation thereof. One is variation in the first heart sound and the other is varying interauricular space.

Variable First Sound.—On listening to the first heart sound in patients with complete block I have observed a variability in its intensity and quality. This has also been noted by others and has been commented on by Carter and Howland [13] as follows:

> The first sound is usually not very loud. From time to time, however, there is a marked accentuation of this sound. . . . the very striking occasional accentuation of the first sound of the heart was a conspicuous feature and was interpreted as being due to the synchronous systole of auricle and ventricle, although auricular systole falling in the long diastolic pauses could not be made out.

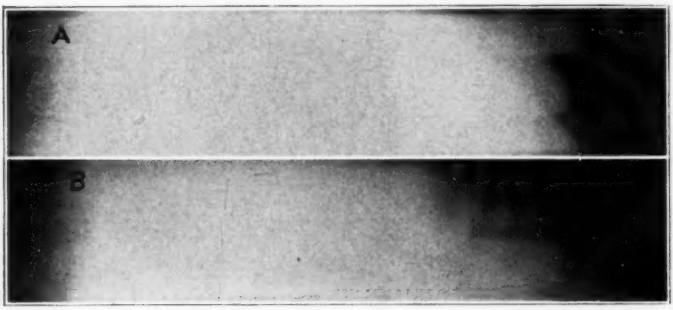

Fig. 5.—Roentgen-kymograms taken in the same manner as that shown in figure 4, but with one slit only, over the point of maximum movement on left ventricular border. Both show variability of the ventricular curve from cycle to cycle. *A* shows one complete ventricular cycle between the parts of two others. There are four auricular systoles shown, the third one coming too late in ventricular diastole to add anything to the intraventricular blood volume which apparently is much less than the volume at the preceding and succeeding systoles as indicated by the lesser ventricular distention of the intermediate cycle. *B* shows two complete ventricular cycles and five auricular systoles, the fourth one of which occurs late in diastole of the second ventricular cycle and appears to have produced a small "tip" on the ventricular curve just before systole.

An equally reasonable explanation of this occasionally accentuated first sound is that it results from ventricular contraction on an unusually large volume of blood. Simultaneous blood pressure readings might elucidate this point, as also might pulse tracings. But in respect to the

13. Carter, E. P., and Howland, J.: A Note Upon the Occurrence of Congenital Atrioventricular Dissociation: Report of a Case of Congenital Complete Heart Block, Bull. Johns Hopkins Hosp. **31**:351 (Oct.) 1920.

latter, the mechanical factor introduces elements which render it almost impossible to place much reliance on small differences in the shape or size of arteriograms. At this point, however, I wish to remark that the shape of the arteriogram in complete heart block seems rather constant even with different machines in the hands of different investigators.[14] These all show a small, if any, dicrotic notch and a gradual return to the base line (fig. 2).

Variable Interauricular Space.—When complete atrioventricular dissociation has become established, the upper chambers, while they beat at their own rhythm, are not uninfluenced by ventricular systole. Wilson and Robinson [15] studied this phenomenon and summarized the literature. They observed that "the interauricular periods during which a ventricular systole occurred were shorter than those following the ventricular contraction." This was especially noticeable when the auricular rate was slow, and has been explained by Erlanger and Blackman [16] as due to "variations in vagal tone, vagus inhibition increasing with each arterial pulse and diminishing again between pulses."

In addition to this explanation I wish to offer another reason for variable interauricular periods; namely, different intra-auricular pressures depending on the volume of blood (amount of resistance) in the ventricle. This assumes that the auricular muscle behaves like other muscle and contracts more strongly, having an automatic rhythm, more frequently, when it meets with an increasing intraventricular pressure on succeeding contractions. Erlanger and Blackman [16] found that "the first auricular cycle following a ventricular contraction is long, but that the successive auricular cycles shorten until the ventricles again contract."

This point is illustrated in figure 6, which reproduces an electrocardiogram taken in a case of incomplete and variable heart block. In lead 2 is shown a period of ventricular asystole lasting for more than four seconds during which six auricular systoles occur. The first two P waves are eighteen twenty-fifths of a second apart and the succeeding waves occur at shorter and shorter intervals until the last two are separated by an interval of only sixteen twenty-fifths of a second.

14. Mackenzie, J.: Diseases of the Heart, ed. 3, London, H. Frowde, 1921, p. 274. Hewlett, A. W.: Pathological Physiology of Internal Diseases, New York, D. Appleton & Company, 1923, p. 66.

15. Wilson, F. N., and Robinson, G. C.: Heart Block; I. Two Cases of Complete Heart Block Showing Unusual Features, Arch. Int. Med. **21**:166 (Jan.) 1918.

16. Erlanger, J., and Blackman, J. R.: Further Studies in the Physiology of Heart Block in Mammals: Chronic Auriculo-Ventricular Heart Block in the Dog, Heart **1**:177, 1909-1910.

It will be observed that when the ventricle does contract after the long asystole it empties itself with a contraction of ectopic origin. If one credits the auricle with an appreciable power of filling the ventricle it does not seem unreasonable to suppose that six fillings from the auricle produced sufficient distention of the ventricle to stimulate a contraction. In lead 3 (fig. 6) there are shorter periods of ventricular asystole in which three auricular contractions occur, and in each instance the ventricular contraction terminating the long pause is ectopic in origin.

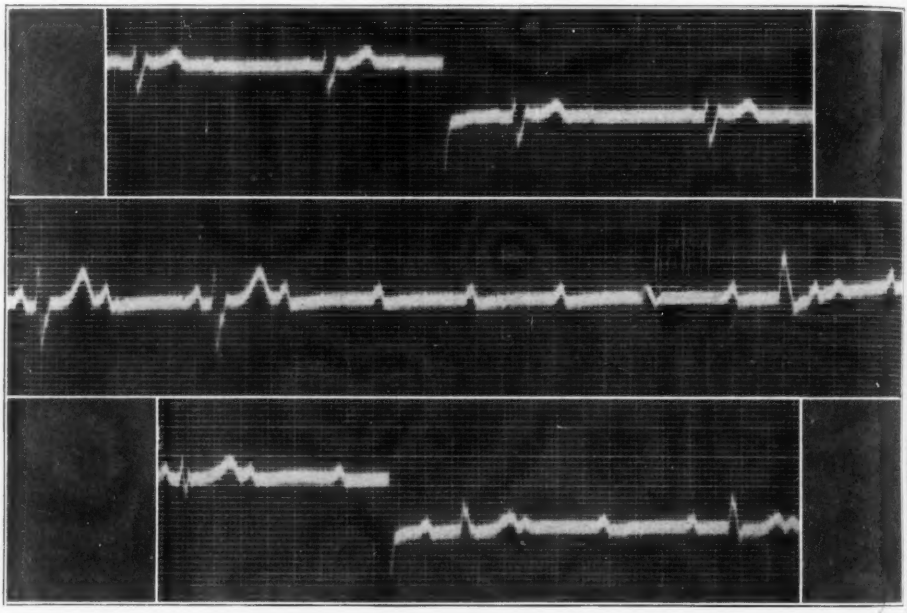

Fig. 6.—Incomplete heart block with variable ventricular response. In the second lead there is a period of ventricular asystole lasting for more than four seconds, during which the auricle contracts six times, the interauricular periods becoming progressively shorter. The long period of ventricular asystole is terminated by a contraction of ectopic origin as are similar but shorter periods in the third lead.

SUMMARY

Two patients with long-standing, complete heart block were studied with a view to obtaining further clinical evidence of the mechanism by which they maintained an adequate circulation with a pulse rate below 50. Increased size of the heart and wide pulse pressure with normal

diastolic blood pressure were noted, as well as wide amplitude of movement of the ventricular border.

Variability of stroke volume was surmised because of: (1) inequality of the first heart sound at successive systoles,[17] (2) variable heights of systolic pressure and (3) the different shape of the roentgen-kymographic curves produced by ventricular systole. This variability seems to be due to the fact that different numbers of auricular systoles occur during ventricular diastole, and a more important rôle in filling the ventricle is attributed to auricular systole than it is customary to assign to it.

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17. Since this paper was submitted for publication, a case similar to these two has been reported by Harris (Heart **14**:289, 1929). From hospital notes made when his patient first came under observation in 1901, it is learned that "the first heart sound is not always the same, sometimes it is louder than otherwise. Sometimes it is very weak, sometimes quite sharp, varying about every four to six beats." Dr. Harris now records that "the first sound varies in intensity at the apex, as it was noted to vary 28 years ago." The blood pressure in his case was 202 systolic and 120 diastolic.

THE TREATMENT OF PNEUMONIA BY INHALATION OF CARBON DIOXIDE

I. THE RELIEF OF ATELECTASIS *

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The problem of pneumonia is peculiar. The pathogenic organisms involved are as well known as those of typhoid or of diphtheria. Yet the mortality from such diseases as typhoid and diphtheria has been reduced far toward the vanishing point, while the mortality from pneumonia per hundred thousand of the population is almost the same as it was fifty years ago.

This lack of progress in the prevention and cure of pneumonia is the more noteworthy in view of the fact that the problem has been attacked as actively as that of other diseases by many able investigators using the methods of bacteriology, serology and preventive medicine. Thus the idea suggests itself that pneumonia may involve some factor that is not concerned in the other diseases and is not to be overcome by the methods effective against them. The factor peculiar to pneumonia may require treatment along a special line.

There is such a factor. It is one with which the internist is usually little concerned. For this reason it was long overlooked in pneumonia and has now only come to light through observations on the pneumonia following surgical operations. It is a factor with which surgeons are familiar; namely, occlusion of an infected organ and lack of drainage.

This new conception of pneumonia is that, as the infection takes place by way of the respiratory passages, it is of critical importance to keep

* Submitted for publication, July 7, 1929.

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these passages open and drained. The bronchoscope has even been used for this purpose. According as the airways are closed or open, the infection is influenced to become acute or is ameliorated. This influence is exactly the same as that of the drainage or occlusion of a localized infection in any other part of the body.

Nature has provided the lungs with several protective devices and reactions. The most obvious is the cough reflex by which irritating foreign bodies are removed. Less obvious, but more constantly acting, are the movements of respiration which are probably accompanied by peristaltic contractions and relaxations of the air tubes. The mucosa lining these tubes bears cilia which produce a continual flow of secretion from the depths of the lungs outward.

Occlusion of an air tube puts all of these mechanisms for the clearing of the lungs out of action. The air in the occluded portion of the lung is soon absorbed, and the alveoli are deflated and collapsed. They are then gradually filled by accumulation of secretion. The conditions resulting are in all respects favorable to the development of micro-organisms and, correspondingly, unfavorable both to the general defenses of the body and the special defenses of the lungs. It is a highly significant fact, as revealed by experiment, that in order to induce pneumonia in dogs it is not enough merely to introduce the pathogenic organisms into the lungs; it is essential also to narcotize the animals so deeply that the cough reflex is abolished and respiration is depressed. In general, depressed or shallow breathing tends to permit the development of pneumonia, and deep breathing with full ventilation of the lungs tends strongly to inhibit it.

ATELECTASIS AS A FACTOR IN PNEUMONIA

The critical importance of occlusion and collapse of the lung in the development of pneumonia might not have been discovered for a long time if investigation of another condition had not brought it to light. This was the occurrence of some degree of collapse of the lung in at least 10 per cent of all patients after surgical operations. The condition is seen particularly in patients who have undergone abdominal operations and whose breathing is thereafter impeded by the pain of the wound.

In tracing this matter still further it appears probable that the mechanism of collapse of the lung or, as it is better termed, atelectasis or apneumatosis (Coryllos), would not have been solved except for the fact that it was observed that this condition also results from the occlusion of a bronchus in diphtheria and from the plugging of a bronchus by a foreign body entering through the larynx and the trachea.

Thus, the evidence up to this point runs: Obstruction of a bronchus induces atelectasis. Atelectasis often follows surgical operations and is

the condition precedent to postoperative pneumonia. Atelectasis gives to pneumonia the character of an occluded and undrained infection. This is the conception which investigation led Coryllos and Birnbaum [1] to formulate. Pneumonia is, in fact, as they define it, a "pneumococcic atelectasis."

Meanwhile, along other lines, the investigations of Henderson and Haggard resulted in the discovery [2] that inhalation of carbon dioxide is under several different clinical conditions, a preventive of pneumonia. The explanation of this effect is now found in the fact that deep breathing induced by inhalation of carbon dioxide dilates the lungs and thus prevents or relieves atelectasis. The principal conditions in which atelectasis and pneumonia are associated and in which inhalation of carbon dioxide is indicated as a preventive are as follows:

ATELECTASIS AND PNEUMONIA IN THE NEW-BORN

Before birth the lungs are normally atelectatic. Although the first cry is the sign that the lungs have been at least partially distended, it is fairly common for parts of the lungs to remain undistended for a considerable time. Such a continuance of atelectasis is recognized as predisposing to pneumonia.[3] To overcome a continuance or recurrence of the condition it is an ancient custom to make the child cry for fifteen minutes or more twice a day. The substitution of inhalation of 5 per cent carbon dioxide would be more in accord with the teachings of physiology. Such an inhalation has in fact been introduced by Henderson [4] as the most effective means of overcoming asphyxia in the new-born and has been widely adopted. It is probable that the routine use of this inhalation on all infants, those that breathe spontaneously, but often incompletely, as well as those which do not breathe without some additional stimulus, would go far to eliminate the occurrence of pneumonia during the first few weeks of life.

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1. Coryllos, Pol N., and Birnbaum, G. L.: Lobar Pneumonia Considered as Pneumococcic Lobar Atelectasis of the Lung; Bronchoscopic Investigation, Arch. Surg. **18**:190 (Jan.) 1929; Bull. New York Acad. Med. **4**:384 (March) 1928.

2. Henderson, Y., and Haggard, H. W.: Hyperventilation of the Lungs as a Prophylactic Measure for Pneumonia, J. A. M. A. **92**:434 (Feb. 9) 1929. Henderson, Y.; Coryllos, P. N.; Haggard, H. W.; Birnbaum, G. L, and Radloff, E. M.: The Relief of Experimental Pneumonia, Proc. Nat. Acad. Sc., Science **69**:502 (May) 1929; The Production and Relief of Atelectasis of Pneumonia, Am. J. Physiol. **90**:317 (Oct.) 1929. Henderson, Y.; Coryllos, P. N.; Holmes, G. W., and Scott, W. J. M.: Symposium on Atelectasis and Pneumonia, J. A. M. A. **93**:96 (July 13) 1929.

3. Holt, L. E., and Howland, J.: Diseases of Infancy and Childhood, part 2, ed. 8, Chapters 1 and 2, New York, D. Appleton & Company, 1922.

4. Henderson, Y.: The Prevention and Treatment of Asphyxia in the New-Born, J. A. M. A. **90**:583 (Feb. 25) 1928.

POSTOPERATIVE PNEUMONIA

A death from pneumonia occurs now on the average, even in the best surgical practice, after each 240 major operations.[4a] Nonfatal pulmonary complications occur frequently. It was shown, however, in papers of the highest importance for the development of this subject, by Scott and Cutler [5] in America and by Dzialoszinski with Meyer [6] and by Fisher [7] in Germany, that liability to postoperative atelectasis, massive, lobar or lobular, and to the pneumonia which frequently ensues, may be greatly reduced, indeed almost eliminated, by the routine administration of carbon dioxide at the termination of anesthesia and operation. That the benefit is due to the effects of carbon dioxide, rather than to the oxygen administered with it, is indicated by the fact that in German surgical practice the carbon dioxide is mixed merely with air without the addition of oxygen. The prophylactic effect of carbon dioxide in the prevention of postoperative pulmonary complications is clearly due to the full inflation of the lungs by the deep breathing induced by the inhalation.

It is probable that many previous observers have had premonitions on this matter; for Osler and McCrae [8] said: "The diagnosis of massive collapse of the lung after operation or injury may be difficult, especially [its differentiation] from lobar pneumonia. . . . In treatment, change in position . . . and encouraging the patient to breathe deeply help in prevention." Meltzer [9] had premonitions of this sort, but he was opposed to the conception, advocated in this country by Henderson,[10] of the physiologic and therapeutic control of respiration by carbon dioxide.

4a. Smith, M. K., and Morton, P. C.: Postoperative Pneumonia, Arch. Surg. **18**:2167 (May) 1929.

5. Scott, W. J. M., and Cutler, E. C.: Postoperative Massive Atelectasis, J. A. M. A. **90**:1759 (June 2) 1928. Elwyn, H.: Postoperative Pneumonia, J. A. M. A. **8**:384 (Feb. 2) 1924. Sise, L. F.; Mason, R. L., and Bogan, I. K.: Prophylaxis of Postoperative Pneumonia: Preliminary Report of Some Experiments After Upper Abdominal Operations, Anesth. & Analg. **7**:187 (May-June) 1928.

6. Dzialoszynski, A.: Apparatus zur Kohlensäureinhalation und bildliche Darstellung der Kohlensäureanwendung am Kranken, Deutsche Ztschr. f. Chir. **205**:22, 1927.

7. Fisher, E.: Prevention of Postoperative Lung Complications by Inhalation of Carbon Dioxide, Zentralbl. f. Gynäk. **52**:2010 (Aug. 11) 1928.

8. Osler: Principles and Practice of Medicine, revised by Thomas McCrae, ed. 10, New York, D. Appleton & Company, 1926, p. 659.

9. Meltzer, S. J.: Ueber eine Methode zur experimentellen Erzeugung von Pneumonie und ueber einige mit dieser Methode erzielte Ergebnisse, Berl. klin. Wchnschr., July 20, 1914, p. 1351.

10. Henderson, Y.: Fatal Apnoea and the Shock Problem, Bull. Johns Hopkins Hosp. **21**:235 (Aug.) 1910.

The inhalation of carbon dioxide in connection with anesthesia was introduced by Henderson, Haggard and Coburn [11] as a means of stimulating breathing, particularly for the purpose of inducing rapid elimination of the anesthetic after operation. An even more important result of such inhalation is the prevention of postoperative atelectasis and pneumonia.

PNEUMONIA AFTER ASPHYXIA

Experience has demonstrated that the treatment for carbon monoxide asphyxia by the inhalation of a mixture of oxygen and carbon dioxide, as introduced by Henderson and Haggard [12] a few years ago, not only is effective in the relief of asphyxia and the removal of carbon monoxide from the blood, but has resulted also in a notable decrease of postasphyxial pneumonia.

The occurrence of râles, edema, bronchopneumonia and lobar pneumonia in patients who have survived carbon monoxide asphyxia without the inhalational treatment has been noted by a number of observers. Their observations were summarized by Hamilton [13] in the statement that "evidence of injury to the lungs is shown in the fairly large proportion of the victims of gassing who have an excess of fluid in the respiratory tract." Drinker and Cannon [14] found in 1923, before the inhalational treatment was introduced, that the hospital records were incomplete regarding such cases, but that they indicate the probability that some degree of bronchopneumonia must be present in nearly all patients who do not succumb immediately following asphyxia by city gas. In contrast, among many hundreds of patients, of whose cases we have reports, treated in recent years with the inhalation of oxygen and carbon dioxide, not a single case of subsequent pneumonia has occurred.

In experiments on dogs asphyxiated with carbon monoxide it was found that animals resuscitated by the inhalation of carbon dioxide make

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11. Henderson, Y.; Haggard, H. W., and Coburn, R. C.: Administration of Carbon Dioxide After Anesthesia and Operation, J. A. M. A. **76**:672 (March 5) 1921. Henderson, Y.; Haggard, H. W., and Coburn, R. C.: Acapnia Theory, J. A. M. A. **77**:424 (Aug. 6) 1921.

12. Henderson, Y., and Haggard, H. W.: The Treatment of Carbon Monoxide Asphyxia by Means of Oxygen Plus Carbon Dioxide Inhalation, J. A. M. A. **79**:1137 (Sept. 30) 1922. Henderson, Y.: Resuscitation from Carbon Monoxide Asphyxia from Ether or Alcohol Intoxication, and from Respiratory Failure Due to Other Causes, J. A. M. A. **83**:758 (Sept. 6) 1924. Henderson, Y., and Haggard, H. W.: Noxious Gases, Chemical Catalog Co., 1925.

13. Hamilton, Alice: Industrial Poisons in the United States, New York, The Macmillan Company, 1925, p. 373.

14. Drinker, C. K., and Cannon, W. B.: Carbon Monoxide Asphyxia: The Problem of Resuscitation, J. Indust. Hyg. **4**:463, 1922-1923.

a complete recovery without pulmonary complications. On the other hand, in animals that are not thus resuscitated the lungs are found at autopsy to be "edematous, and the alveoli to be filled with an almost homogeneous coagulum of albumin-rich fluid. Vascular stasis is also marked in some cases, although there is only a slight cellular inflammatory reaction and a few widely scattered small hemorrhages." [15]

No attempt will be made here to explain how asphyxia induces such a condition in the lungs. It is sufficient for present purposes to note the fact that, both in experiments on animals and in observations on patients, inhalation of carbon dioxide, simultaneously with the relief of asphyxia by means of oxygen, counteracts the tendency for this condition to give rise to postasphyxial pneumonia.

ATELECTASIS IN PNEUMONIA

Atelectasis, or apneumatosis (Coryllos), known in the first half of the last century and then almost forgotten, was described again in 1908 and 1910 by W. Pasteur [16] in cases of diphtheria with paralysis of the diaphragm. The clinical observations of Jackson and Lee [17] showed that bronchial obstruction by preventing the ventilation of a part of the lung permits a gradual absorption of the air within its alveoli and thus results in the deflation and collapse of a lobe or lobules or of the whole of one lung. More than fifty years ago, experimental evidence was obtained by Mendelsohn [18] and by Lichtheim [19] that the insertion of a plug in a bronchus induces atelectasis in the portion of the lung to which it leads. But only recently has this subject been developed on the basis of thorough experimental investigation by Coryllos and Birnbaum.[20]

They have devised plugs consisting of small rubber bags which are inserted in one of the main bronchi or in a branch by means of a bronchoscope and inflated so as to block off the airway completely. The dogs are narcotized with iso-amyl-ethyl barbituric acid to prevent coughing. Unilateral atelectasis develops in a few hours and is demonstrated by means of x-ray pictures. The most striking and most reliable index

15. Quoted from a report on autopsies, in 1922, by Dr. R. A. Lambert, department of pathology, Yale Medical School.

16. Pasteur, W.: Massive Collapse of the Lung, Lancet **2**:1351, 1908 and **2**:1080, 1910.

17. Jackson, Chevalier; and Lee, W. E.: Acute Massive Collapse of the Lungs, Ann. Surg. **82**:364 (Sept.) 1925.

18. Mendelsohn, A., quoted by Lord, F. F.: Diseases of the Bronchi, Lungs and Pleura, Philadelphia, Lea & Febiger, 1915.

19. Lichtheim, L.: Arch. f. exper. Path. u. Pharmakol. **10**:54, 1879.

20. Coryllos, Pol N., and Birnbaum, G. L.: Obstructive Massive Atelectasis of the Lung, Arch. Surg. **16**:501 (Feb.) 1928.

of the degree of atelectasis is afforded by displacement of the heart and mediastinum toward the side affected. The diaphragm is also elevated on that side and lowered on the side of the normal lung. In the dog the displacement of the heart is much greater than is possible in man, owing to the more rigid mediastinum in man, while the distortion of the diaphragm is greater in man than in the dog.

Following up this study of the effects of mechanical obstruction of the airways, Coryllos and Birnbaum [2] showed that lobar pneumonia is essentially a pneumococcic atelectasis. In their experiments, dogs which are deeply narcotized with iso-amyl-ethyl barbituric acid receive through the bronchoscope into one bronchus and its branches a small volume of a virulent culture of pneumococci concentrated by the centrifuge from a larger volume. The next day, a unilateral pneumococcic atelectasis with marked displacement of the heart toward the affected lung is found. This condition develops into a typical unilateral pneumonia with consolidation and hepatization. In the large majority of cases the disease terminates fatally in from one to three days.

Coryllos and Birnbaum also correlated this experimental evidence with clinical observations demonstrating that atelectasis is a critical factor in pneumonia. Thus, both experimental and clinical evidence indicates that in the development of pneumonia the first stage after infection is a catarrh which plugs the airways, great or small, with thick, sticky secretion and prevents their ventilation by the movements of respiration. The normal drainage is thus stopped, the air is absorbed, the lung or lobe or lobules are collapsed and an occluded area of infection is produced. In such areas, and only in such areas, pneumonia develops. The condition is sometimes successfully relieved in patients by aspirating the bronchi through a bronchoscope.

In pneumonia the heart is not displaced toward the normal lung, as it would be if the current conception were correct. In medical pneumonia, as in postoperative pneumonia, the heart is always displaced toward the pneumonic lung. This fact has now been observed also in pneumonia in children by Tallerman and Jupe.[20a]

EXPERIMENTAL WORK

The Relief of Atelectasis.—The first series of experiments to be reported here was made for the purpose of determining the effectiveness of the inhalation of carbon dioxide in redilating a lung that had been collapsed by simple obstructive atelectasis without infection. In these experiments, twenty-four large dogs, from 12 to 25 Kg. in weight, were used. They received, by intraperitoneal injection, 0.5 cc. per kilogram of a freshly made 10 per cent solution of iso-amyl-ethyl bar-

20a. Tallerman, K. H., and Jupe, M. H.: Displacement of Heart in Pneumonia in Childhood, Arch. Dis. Childhood **4**:155 (Aug.) 1929, quoted in J. A. M. A. **93**:1099 (Oct. 5) 1929.

bituric acid. Within fifteen minutes this induced, in nearly all cases, a deep narcosis lasting from twelve to twenty-four hours. An x-ray picture was taken to make sure that the heart and lungs were in normal condition and position. By means of a bronchoscope a rubber bag, similar to those used by Coryllos and Birnbaum but somewhat larger and fitted with a valve from a bicycle tire, was then inserted into the right bronchus and inflated with water so as to shut off as nearly as possible all the branches of the bronchus. In some of the earlier experiments a strong solution of sodium bromide or sodium iodide was used to inflate the bag; but it was found that if any of this solution escaped into the lung, it caused acute irritation or even immediate death. Water produces no such effect.

As soon as the bronchial plug was in place, the dog was laid in a special holder similar to that used by Coryllos and Birnbaum, so that its position could be adjusted as precisely as possible, and an x-ray picture was taken. The animal was then laid on its right side on the floor, where it remained in profound narcosis for many hours.

The next day, a second x-ray picture was taken and showed in all cases a degree of atelectasis and of displacement of the heart corresponding to the number of branches of the bronchus occluded; for atelectasis develops only in an area the airway of which is completely shut off. With the dog under ether anesthesia and by means of the bronchoscope the plug was withdrawn from the bronchus and the animal was placed in an atmosphere of air to which from 5 to 7 per cent of carbon dioxide was added. For this purpose a chamber 12 by 9 feet and 7 feet high (3.6 by 2.7 by 2.1 meters) was used. Its walls consisted of window sash; the joints were made airtight with soft asphalt. Beneath the wooden floor and above the wooden ceiling were layers of soft asphalt. It had double doors to form an air lock and was cooled by a coil of pipes (automobile radiator) connected to the main water supply of the laboratory and draining into a sink in the chamber. Carbon dioxide gas was run into this chamber from a cylinder of liquefied "carbonic acid" through a meter and was mixed with the air by an electric fan. The contents of the chamber were determined at intervals by gas analysis with an Orsat analyzer. Usually the initial concentration was about 7 per cent and dropped to 5 or 6 per cent in the course of an hour or two. From four to six animals were put into the chamber together and were allowed to move about freely. They breathed deeply but appeared comfortable and sometimes slept.

After the animals had been in the chamber from thirty to sixty minutes they were removed from it and another set of x-ray pictures was taken. These pictures were in striking contrast to those taken prior to the period in the chamber. They showed a restoration of a practically normal condition in the thorax.

The observations of Coryllos and Birnbaum [20] in earlier series of experiments have shown that simple obstructive atelectasis, such as these cases presented, usually clears up only in the course of several hours. It is therefore highly significant that after being in this chamber and inhaling carbon dioxide for only thirty to sixty minutes—shorter periods would probably have been sufficient—the atelectasis was in all cases relieved and the heart was restored to its normal position. These observations confirm experimentally the similar clinical observations of Scott and Cutler.[5] The changes in the thorax, and particularly the displacement toward the atelectatic right lung of the line of the left

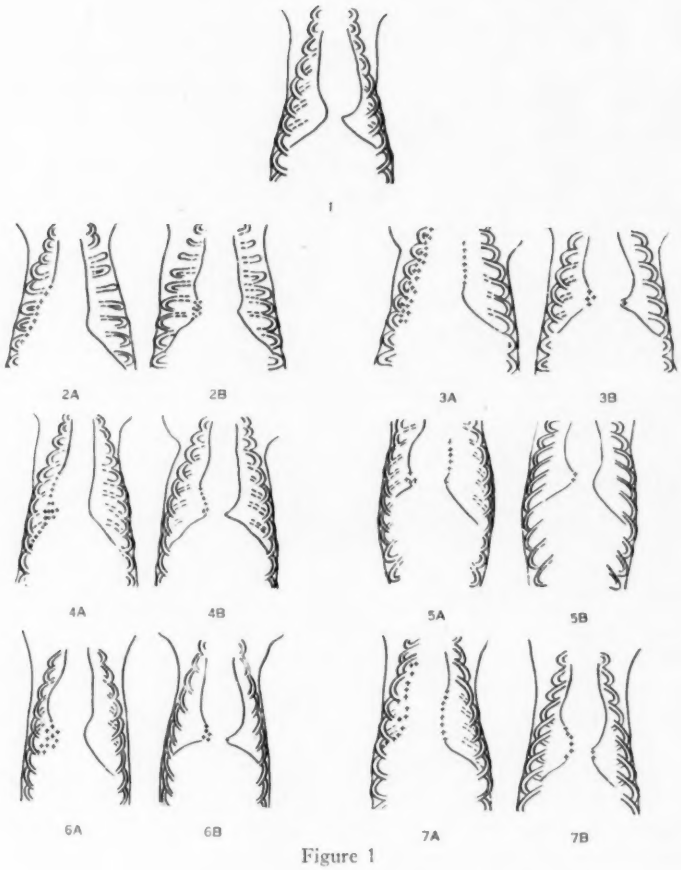

Figure 1

EXPLANATION OF FIGURE 1

Fig. 1.—Relief of atelectasis by inhalation of carbon dioxide (drawings traced from x-ray films): 1, outline of the normal thorax of a dog, weighing 15 Kg., showing the ribs, heart and diaphragm. Normal x-ray pictures were made from all the animals, but as all these pictures are essentially similar, only one is here reproduced. 2 *A*, the thorax of dog AJJ, weighing 15 Kg., twenty-two hours after obstruction of the right common bronchus. Note the displacement of the heart, particularly of the left border (at the right in the drawing) away from the normal lung and toward the atelectatic lung. In this and succeeding pictures, cloudy outlines are indicated by ++++. 2 *B*, after removal of the bronchial plug, the animal was kept in a chamber containing air and an average of 6 per cent carbon dioxide for fifty minutes. This picture was then taken. Note that the left border of the heart (at the right in the picture) has returned to nearly the normal position and that the right border of the heart (on the left in the picture) has a distinct outline through most of its extent and is in the normal position. 3 *A*, the thorax of dog AL, weighing 26 Kg., twenty-one hours after obstruction of the right common bronchus. The right lung is almost completely collapsed and the heart is displaced, so that its left border is nearly in the midline. The right side of the diaphragm is obscured and the left side is distorted downward in a manner characteristic of contralateral atelectasis. 3 *B*, after removal of the plug from the bronchus, the animal was kept under light ether anesthesia for twenty or thirty minutes during which time it struggled vigorously. This picture was then taken and shows that the atelectasis had almost completely cleared up, allowing the heart and diaphragm to return to their normal positions. The x-ray pictures, from which 3 *A* and 3 *B* are traced, are reproduced in figure 2. 4 *A*, the heart of dog AJ, weighing 15 Kg., twenty-two hours after the right common bronchus was obstructed. The picture shows extreme atelectasis of the right lung with displacement of the heart and distortion of the diaphragm. 4 *B*, after removal of the plug from the bronchus, the animal was placed for forty-five minutes in 6 per cent carbon dioxide; this picture was then taken. It shows that the atelectasis had cleared up and that the heart and diaphragm had returned to their normal positions. 5 *A*, the thorax of dog AM, weighing 14 Kg., twenty-one hours after obstruction of the right common bronchus. There is atelectasis in the greater part of the right lung with displacement of the heart and distortion of the diaphragm. 5 *B*, after removal of the plug from the bronchus the animal was placed in a chamber with 6 per cent carbon dioxide for forty minutes. The picture shows an almost complete return of the heart and diaphragm to the normal position. 6 *A*, the thorax of dog AN, weighing 15 Kg., nineteen hours after obstruction of the right common bronchus. The extent of atelectasis in the right lung is indicated by the displacement of the heart and the distortion of the diaphragm. 6 *B*, after removal of the plug from the bronchus, the animal was placed for forty minutes in 6 per cent carbon dioxide. At the end of this time, as the picture shows, the atelectasis had cleared up and the heart and diaphragm had returned to their normal positions. 7 *A*, the thorax of dog AO, weighing 13 Kg., nineteen hours after obstruction of the right common bronchus. There is an extreme degree of atelectasis. 7 *B*, after removal of the plug from the bronchus, the animal was placed for forty minutes in 6 per cent carbon dioxide. As the picture shows, the atelectasis at the end of this time had cleared up and the heart and diaphragm had returned to their normal position.

border of the heart, are shown for six experiments in figure 1. The significant details of the experiments are given in the legend.

As the bronchi are innervated by the vagi, three experiments were tried to determine whether these nerves may play a part in producing atelectasis. After the animal was narcotized, the right vagus was cut and the peripheral end stimulated; but no effects were observable in x-ray pictures after section or during stimulation. The bronchus was then plugged and atelectasis was developed precisely as in a lung with normal innervation. Next day, the atelectasis was relieved by the inhalation of carbon dioxide, precisely as in animals in which the nerve was not cut. These observations, so far as they go, indicate that the innervation of the lung is not involved in the production or relief of atelectasis, in agreement with Fontaine and Herrmann.[21]

Clear evidence that the main factor in redistending an atelectatic lung is deep breathing rather than the effects of carbon dioxide on the circulation, is afforded particularly by one experiment in which vigorous breathing was induced, after removal of the bronchial plug, by keeping the animal under light ether anesthesia for nearly half an hour. It struggled vigorously, and drew many deep breaths. In an x-ray picture taken immediately thereafter, the atelectasis had cleared up, while in the picture previous to this treatment the atelectasis was extreme. These pictures, shown in figure 2, afford conclusive evidence that it is deep breathing and not an effect of carbon dioxide on nervous or vascular mechanisms which clears up atelectasis.

The Relief of Pneumonia.—In this series of experiments, twenty-eight dogs were given the usual narcotizing dose of iso-amyl-ethyl barbituric acid. Prof. Leo F. Rettger supplied a virulent culture of pneumococcus type II from the Yale Laboratory of Bacteriology. A volume of 1.5 cc. of the culture per kilogram of body weight of the dog to be infected was centrifugated and decanted down to 0.2 cc. per kilogram of the animal's weight; the sediment was mixed in this volume. After insertion of the bronchoscope into the right bronchus, this concentrated suspension of pneumococci was insufflated into the bronchus and its branches.

After a preliminary group of experiments on six dogs, for practice in technic and procedure and for untreated controls, a series of experiments was carried out on twenty-two dogs. In this series, two dogs were found dead, chiefly from iso-amyl-ethyl barbituric acid poisoning, on the morning following narcotization, and four failed to develop pneumonia. Of the remaining sixteen all developed pneumonia—in most cases so severely that, judging by the six control animals and by the experience of Coryllos and Birnbaum, few if any would have survived. However, after spending various periods from two to twenty-four hours in from 5 to 7 per cent carbon dioxide in the chamber, all except three of the sixteen made a complete recovery. Even in those which died, autopsy showed that in two cases the cause of death was the suppurative pneumonitis, probably due to *Bacillus coli*, as was observed by Coryllos and Birnbaum, and as occurred also in some of our dogs a day or two after withdrawal of the bronchial plug in the preceding series of experiments.

More significant than such statistics, however, are the x-ray pictures, illustrations of which are given in figures 3 and 4, and outline drawings in figure 5. These figures and their legends show clearly: (1) that in all these cases of pneu-

21. Fontaine, R., and Herrmann, L. G.: Experimental Studies on Denervated Lungs, Arch. Surg. **16**:1153 (June) 1928.

monia, atelectasis was a striking feature, and (*2*) that under inhalation of carbon dioxide a reinflation of the pneumonic lung occurred in all cases. It is noteworthy, however, that while in all respects, except one, these experiments on pneumonia and its relief appear closely similar to the preceding experiments on atelectasis without infection, in this one feature there is a significant difference between the two sets of experiments. Different times are required. While considerably less than one hour in an atmosphere of carbon dioxide was sufficient to overcome simple atelectasis due to a bronchial plug, two hours, and in some cases twenty-four hours, in this atmosphere was required to reinflate the pneumonic lung.

During the period of inhalation of carbon dioxide the dogs with pneumonia drank, or if too weak to drink by themselves, were assisted in drinking, large amounts of water. This probably aided in their recovery, by overcoming anhydremia.

COMMENT

The observations reported in the two foregoing sections taken together throw light on two important matters: (1) the part which

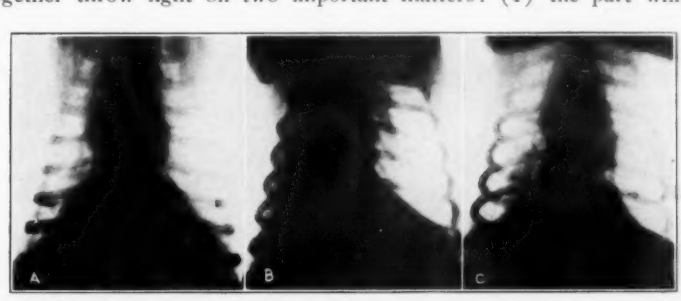

Fig. 2.—The thorax of dog AL: *A*, the normal condition, before the insertion of a plug in the right bronchus; *B*, extreme atelectasis the next day; *C*, half an hour later, reinflation of the right lung and restoration of the heart to the normal position, effected by removal of the plug and by a period of struggling and respiratory excitement under light ether anesthesia. The second and third of these pictures are also shown in outline as 3 *A* and *B* in figure 1.

atelectasis plays in pneumonia, and (*2*) the effectiveness of the inhalation of carbon dioxide as a prophylactic and therapeutic measure against pneumonia.

In relation to the first of these topics the outstanding feature of the observations reported is the similarity of the experiments on pneumonia to those on simple obstructive atelectasis. Not only are the x-ray pictures of atelectasis from bronchial obstruction and pneumonia from intrabronchial infection strikingly alike, but—even more significant—the effects of the inhalation of carbon dioxide in the two series of experiments are closely similar. There can scarcely be any doubt as to the general character of the process involved in the opening up of a lung rendered atelectatic merely by bronchial obstruction without infection.

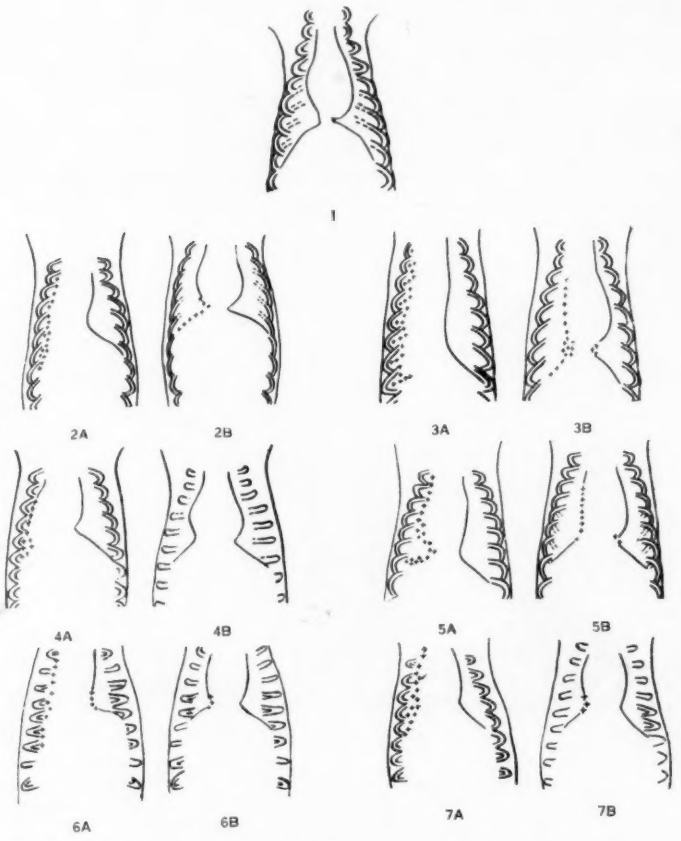

Fig. 3.—Relief of pneumonia by inhalation of carbon dioxide (drawings traced from x-ray films): 1, outline of the normal thorax of a dog, weighing 17 Kg., showing the ribs, heart and diaphragm. This will serve for comparison with the pictures of pneumonia indicated as *A* and of recovery indicated as *B* in the subsequent pictures. *2A*, the thorax of dog PE, weighing 12 Kg., twenty-four hours after insufflation of 6 cc. of the sediment concentrated by the centrifuge from 18 cc. of a culture of pneumococci type II. Note the displacement of the heart toward the pneumonic lung, indicating extreme collapse of the right lung, which was nearly as opaque to x-rays as the heart was. In this and succeeding pictures, cloudy outlines are indicated by ++++. *2B*, the animal was placed in carbon dioxide, of an average concentration of 6 per cent, but showed only slight improvement during the first two hours. After twenty-three hours, however, the pneumonia had to a large extent cleared up and this picture was obtained. The animal made a complete recovery. It was killed four days later and when it underwent autopsy the lungs were found normal. The x-ray pictures, from

EXPLANATION OF FIGURE 3—*Continued*

which *2 A* and *2 B* are traced, are reproduced in figure 4. *3 A*, the thorax of dog PF, weighing 17 Kg., twenty-four hours after insufflation of the sediment concentrated from 25 cc. of the culture of pneumococci. Note the extreme displacement of the heart; the left hand border is almost on the line of the vertebral column. A large part of the right lung was as opaque to x-rays as the heart itself. *3 B*, the animal was placed in carbon dioxide, average concentration of 6 per cent, for two hours, after which this picture was taken. There is an almost complete restoration of the heart to the normal position, but an incomplete clearing up of the lung. The animal was extremely ill and died two hours later. At autopsy considerable areas in the right lung and a part also of the left lung were found to be hepatized. *4 A*, the thorax of dog PG, weighing 20 Kg., twenty-four hours after insufflation of the sediment concentrated from 30 cc. of the culture of pneumococci. There is an intense unilateral pneumonia with displacement of the heart toward the infected lung. *4 B*, the animal was placed in carbon dioxide, average concentration 6 per cent, but made only slight improvement during the first few hours. After twenty-four hours in decreasing concentrations of carbon dioxide from 7 to 4 per cent the picture was taken from which this drawing is traced. It shows that the right lung had largely cleared up, and that the heart had returned to nearly the normal position. The animal appeared entirely well the next day. It was killed and underwent autopsy four days later. The lungs were found normal except for a few small areas of congestion in the upper lobe of the left lung. *5 A*, the thorax of dog PJ, weighing 17 Kg., twenty-four hours after insufflation of the sediment from 25 cc. of the culture of pneumococci. There is displacement of the heart to the right and opacity of the right lung except on its costal border. *5 B*, the animal was placed in carbon dioxide, average concentration 6 per cent, for one and three-fourths hours. This picture was then taken and shows restoration of the heart to a nearly normal position, and a considerable degree of clearing in the right lung. The animal was found dead the next day. On autopsy it was found to have developed a suppurative pneumonitis with a strong fecal odor, probably due to infection by *Bacillus coli*. *6 A*, the thorax of dog PS, weighing 14 Kg., twenty-three hours after insufflation of the sediment from 21 cc. of the culture of pneumococci. There is displacement of the heart to the right and complete opacity at the right lung except along the costal margin. *6 B*, after two hours in carbon dioxide, average concentration 6 per cent, the heart had returned about half way to normal position and the right lung had cleared to a considerable extent, as shown. Before being placed in the chamber this dog showed a rectal temperature of 101 F. After two hours in carbon dioxide its temperature was 99.8 F. The animal appeared entirely well the next day, and was alive and healthy two weeks later. *7 A*, thorax of dog PT, weighing 20 Kg., twenty-three hours after insufflation of the sediment from 30 cc. of the culture of pneumococci. There is displacement of the heart to the right, disappearance of the outline of the right side of the heart and of the right side of the diaphragm and a high degree of congestion in the right lung. *7 B*, after two hours in carbon dioxide, average concentration 6 per cent, the heart had returned to nearly normal position and the right lung had largely cleared, as shown. The rectal temperature before the animal was placed in the carbon dioxide chamber was 102.8 F. At the end of the two hours of inhalation the temperature was 101.2 F. This dog made an uneventful recovery and was alive and well two weeks later.

Therefore the fact that inhalation of carbon dioxide results in a closely similar, even if much slower, opening up of a pneumonic lung affords conclusive proof that atelectasis is a factor in pneumonia. This conclusion is further reinforced by the fact that dogs with pneumonia, which would otherwise prove fatal, are generally restored to health as a consequence of this reopening of the lung. That pneumonia derives its virulent character to a large degree from the fact that it is an occluded infection is also thus proved; for the chief effect of opening up the pneumonic lung under inhalation of carbon dioxide is to provide drainage, although there may also be chemical and bactericidal effects, and influences on the circulation. Once it is reopened the lung may clear itself. As in many surgical infections, so in medical pneumonia, occlusion is the critical morbidic factor. Thus, the thesis of Coryllos and Birnbaum that lobar pneumonia is a pneumococcic atelectasis is completely confirmed.

On the second topic, the effectiveness of inhalation of carbon dioxide as a prophylactic measure against pneumonia, these observations are equally conclusive. The reason that the treatment of carbon monoxide asphyxia by inhalation of oxygen and 5 per cent carbon dioxide prevents a subsequent pneumonia—a fact which we have known for several years but could not previously explain—is now clear. Similarly, the discovery of Scott and Cutler and of German surgeons that inhalation of carbon dioxide at the termination of general anesthesia prevents postoperative pneumonia is confirmed and explained. The value of inhalation of carbon dioxide in the treatment of asphyxia and in connection with anesthesia is shown to be far greater than originally claimed by Henderson and Haggard. They introduced this treatment as a means of stimulating respiration and thus hastening the elimination of carbon monoxide, the anesthetics, and other foreign and toxic volatile substances from the blood. The accessory effect of preventing pneumonia after anesthesia and operation and after asphyxia is more important. If this inhalation proves even partially effective in the treatment of medical pneumonia, that result will become of yet greater importance.

Several hundred patients with pneumonia have been treated with oxygen and 5 per cent carbon dioxide by means of the inhalators employed in resuscitating patients with carbon monoxide asphyxia. In one group of 126 cases, the report shows that only nine patients died, while a number recovered by crisis immediately after the inhalation. Even more important than this low mortality is the fact that of the patients treated early nearly all recovered, while the deaths were nearly all among those treated late. In a much larger group of patients not so treated the mortality was 31 per cent. These observations are to be continued and will be reported in a later paper.

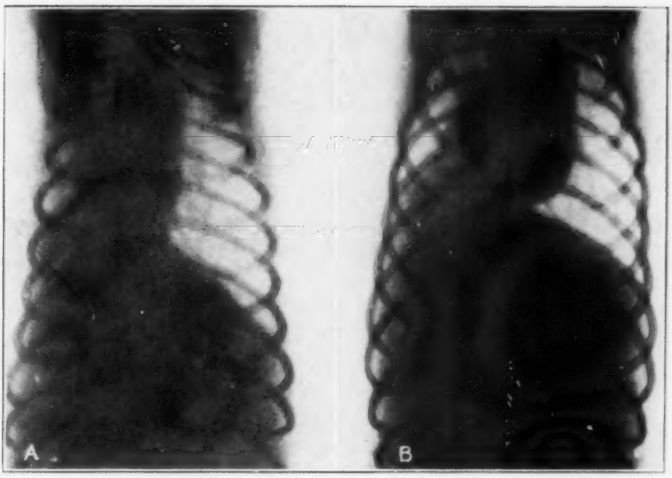

Fig. 4.—*A* shows unilateral pneumonia in dog PE, twenty-four hours after insufflation of pneumococci type II into the right bronchus; *B*, restoration of the heart to the normal position and partial clearing up of the pneumonic right lung after twenty-three hours in 6 per cent carbon dioxide. This animal made a complete recovery. It was killed and underwent autopsy four days later; the lungs were found to be normal. These pictures are also shown in outline in 2 *A* and *B* in figure 3.

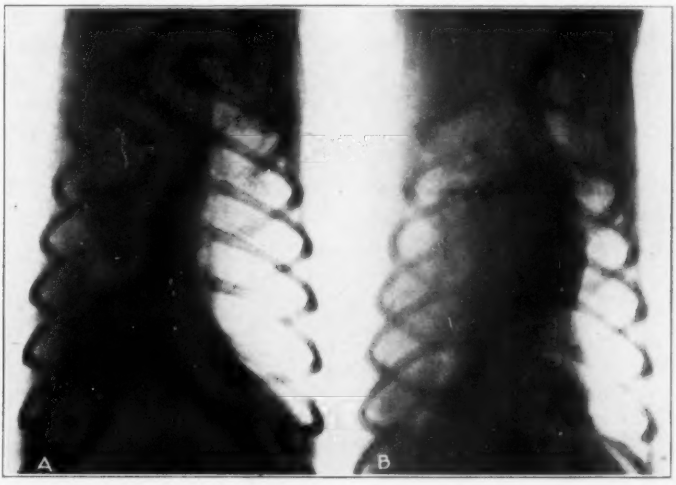

Fig. 5.—*A* shows unilateral pneumonia in dog PF, twenty-four hours after insufflation of pneumococci type II into the right bronchus; *B*, restoration of the heart to the normal position and partial clearing of the pneumonic right lung after inhalation of 6 per cent carbon dioxide for two hours. The animal was extremely ill and died two hours later. These pictures are shown in outline in 3 *A* and *B* of figure 3.

PHYSIOLOGIC EVIDENCE IN ATELECTASIS

Atelectasis presents a number of puzzling subsidiary problems. Is the causation of atelectasis wholly mechanical, as Coryllos and Birnbaum concluded from their investigations? Or, on the other hand, are there nervous and vascular factors in the collapse of the lung? How are the gases, particularly nitrogen, absorbed? Is there any connection between this problem and that of the spontaneous reinflation of the lung after a therapeutic pneumothorax? Is the difference between pneumothorax and atelectasis wholly dependent on the patency or obstruction of the airways? What light does the evidence from the anatomy of the lung and from the experimental physiology of the bronchial innervation throw on these questions?

The physiologic literature affords little help in understanding these problems. We refer to this literature here chiefly in order to be of service to any reader who may wish to consult it in the hope of finding some hint that others have missed. On the anatomic side the excellent recent review by Macklin [22] gives a picture of the lung as a contractile organ permeated with nonstriated muscle tissue. This conception is certainly suggestive. On the side of the physiology of the lung the extensive investigations of Carlson and Luckhardt [23] and the observations of Patterson [24] show that, if the lungs of men and of frogs were entirely alike, the explanation of atelectasis would probably be found in a nervous effect induced through the vagi and resulting in a prolonged contraction of the intrinsic musculature of the lung. This phenomenon, as described by these investigators in the frog, has not, however, been produced experimentally in a mammal.

The literature on the nervous control of the bronchi in mammals has usually had as its background the phenonmena of asthma, as in the paper of Mount,[25] and the pharmacologic relief of the symptoms of that disorder; it helps but little toward an understanding of atelectasis. The long papers of Einthoven [26] and of Beer [27] are the classics in this field.

22. Macklin, C. C.: The Musculature of the Bronchi and Lungs, Physiol. Rev. **9**:1 (Jan.) 1929.

23. Carlson, A. J., and Luckhardt, A. B.: Studies on the Visceral Sensory Nervous System, Am. J. Physiol. **54**:55 (Nov.) 1920; **55**:13 and 31 (Feb.), 212 (March), 366 (April); **56**:72 (May); **57**:299 (Sept.) 1921.

24. Patterson, T. L.: Studies on the Visceral Sensory Nervous System: IX. The Readjustment of the Peripheral Lung Motor Mechanism After Bilateral Vagotony in the Frog, Am. J. Physiol. **58**:169 (Nov.) 1921.

25. Mount, H. T. R.: Experimental Study of the Effects of Stimulation and Section of the Vagal Innervation to the Bronchi, and Their Possible Relation to Asthma, Am. J. M. Sc. **177**:697 (May) 1929.

26. Einthoven, W.: Ueber die Wirkung der Bronchialmuskeln, nach einer neuen Methode untersucht und über Asthma nervosum, Arch. f. d. ges. Physiol. **51**:367, 1892.

27. Beer, Theodor: Ueber den Einfluss der peripheren Vagusreizung auf die Lunge, Arch. f. Anat. u. Physiol., 1892, p. 101.

The work of Haldane [28] and his collaborators comes closer to suggestions of importance than that of most other investigators. It shows that shallow breathing in a normal man may leave considerable areas of the lung unventilated, as evidenced by cyanosis. Doubtless a continuation of the experiment and some accumulation of mucus to form a plug in an air tube would produce atelectasis.

Dunn,[29] and Binger and his collaborators [30] have demonstrated that multiple small emboli experimentally introduced into the pulmonary circulation may induce shallow breathing. Porter and Newburgh [31] showed that irritation of the afferent endings of the vagi in the lungs is the cause of the shallow, rapid breathing in pneumonia. Churchill and Cope [32] gave a similar demonstration for pulmonary congestion and edema. Shallow breathing, according to Meakins,[33] is in turn the cause of anoxemia in pneumonia, for it ventilates the lungs incompletely. All the factors of a vicious circle are thus provided.

Among the papers dealing with the pharmacologic aspects of the bronchi and their innervation, those of Dixon,[34] Trendelenburg [35] and Tiefensee [36] are especially noteworthy. Reviews giving the physiologic

28. Haldane, J. S.: Respiration, New Haven, Conn., Yale University Press, 1922, p. 136.

29. Dunn, J. S.: The Effects of Multiple Emboli in Pulmonary Arterioles, Quart. J. Med. **13**:129, 1920.

30. Binger, A. L.: Experimental Studies on Rapid Breathing: II. Tachypnea, Dependent upon Anoxemia, Resulting from Multiple Emboli in the Larger Branches of the Pulmonary Artery, J. Clin. Investigation **1**:155 (Dec.) 1924. Binger, A. L., and Moore, R. L.: J. Exper. Med. **45**:655, 1927.

31. Porter, W. T., and Newburgh, L. H.: Am. J. Physiol. **42**:175, 1916; **43**: 455, 1917. Porter; Newburgh and Means, J. H.: J. Exper. Med. **24**:583, 1916.

32. Churchill, E. D., and Cope, O.: The Rapid Shallow Breathing Resulting from Pulmonary Congestion and Edema, J. Exper. Med. **49**:531, 1929.

33. Meakins, J.: Harmful Effects of Shallow Breathing with Special Reference to Pneumonia, Arch. Int. Med. **25**:1 (Jan.) 1920.

34. Dixon, W. E., and Brodie, T. G.: Contributions to the Physiology of the Lungs: I. The Bronchial Muscles, Their Innervations and the Action of Drugs upon Them, J. Physiol. **29**:97, 1903. Dixon, W. E., and Ransom, F.: Bronchodilator Nerves, J. Physiol. **45**:413, 1913. Dixon, W. E., and Hoyle, J. C.: Studies in the Pulmonary Circulation: I. The Vaso-Motor Supply, J. Physiol. **65**:299 (June 24) 1928. Dixon, W. E., and Hoyle, J. C.: Studies in the Pulmonary Circulation: I. The Action of Adrenaline and Nicotine, J. Physiol. **67**:77 (Feb. 28) 1929.

35. Trendelenburg, P.: Physiologische und pharmakologische Untersuchungen an der isolierten Bronchialmuskulatur, Arch. f. exper. Path. u. Pharmakol. **69**:79, 1912; Versuche an der isolierten Bronchialmuskulatur, Zentralbl. f. Physiol. **26**:1, 1913.

36. Tiefensee, K.: Pharmakologische Studien auf der Bronchialmuskulatur: I. Methodik, Arch. f. exper. Path. u. Pharmakol. **139**:129, 1929. II. Ueber die Bedeutung der Blutbeschaffenheit für den Tonus der Bronchialmuskeln und ihr Ansprechen auf Gifte **139**:139, 1929.

and pharmacologic literature have been published by Starling in Schafer's Textbook of Physiology,[37] by Boruttau in Nagel's handbook,[38] Schenck in Tigerstedt's handbook,[39] and Skramlik [40] in volume 2 of the excellent handbook now under publication, edited by Bethe and others. Volume 2 of this handbook also contains monographs dealing with the anatomy of the lungs by Felix,[41] the mechanics of respiration by Rohrer,[42] the chemistry of the respiratory exchange by Liljestrand,[43] the pathologic physiology of the airways by Amersbach,[44] the pathologic physiology of respiration by Hofbauer [45] and the pharmacology of respiration by Bayer.[46]

A survey of all this literature affords, however, little direct evidence that atelectasis can arise directly from nervous influences on the lung. At present, the only clearly demonstrated causes are shallow breathing and the accumulation of mucus, resulting in the mechanical blocking of the air tubes.

SUMMARY AND CONCLUSIONS

1. As the background for this study, the following facts are cited:

(*a*) If the lungs are not fully distended soon after birth, pneumonia is likely to develop.

(*b*) After surgical operations, massive, lobar or lobular atelectasis of the lung is a rather frequent occurrence, and is the condition from which postoperative pneumonia develops. This atelectasis or, better, apneumatosis is prevented and relieved, and the risk of pneumonia is eliminated, by the inhalation of carbon dioxide.

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37. Starling, E. H.: The Muscular and Nervous Mechanism of the Respiratory Movements, Text-book of Physiology, vol. 2, New York, The Macmillan Company, 1900, p. 274.

38. Boruttau, Heinrich: Die Atembewegungen und ihre Innervation: IV. Die Innervation der Atembewegungen, in W. Nagel: Handbuch der Physiologie des Menschen, Braunschweig, F. Vieweg und Sohn, 1909, vol. 1, p. 29.

39. Schenck, F.: Atembewegungen, Handbuch der physiologischen Methodik, vol. 2, Leipzig, 1908.

40. Von Skramlik, Emil: Die Physiologie der Luftwege, Handbuch der normalen und pathologischen Physiologie, ed. by Bethe, Bergmann Embden and Ellinger, Berlin, Julius Springer, 1925, vol. 2, p. 128.

41. Felix, Walther: Anatomie der Atmungsorgane, Handbuch der normalen und pathologischen Physiologie, vol. 2, p. 37.

42. Rohrer, Fritz: Physiologie der Atembewegung, Handbuch der normalen und pathologischen Physiologie, vol. 2, p. 70.

43. Liljestrand, G.: Chemismus des Lungengaswechsels, Handbuch der normalen und pathologischen Physiologie, vol. 2, p. 190.

44. Amersbach, K.: Patho-Physiologie der Luftwege, Handbuch der normalen und pathologischen, Physiologie, vol. 2, p. 307.

45. Hofbauer, Ludwig: Pathologische Physiologie der Atmung, Handbuch der normalen und pathologischen Physiologie, vol. 2, p. 337.

46. Bayer, Gustav: Pharmakologie der Atmung, Handbuch der normalen und pathologischen Physiologie, vol. 2, p. 455.

(*c*) The inhalation of 5 per cent carbon dioxide in oxygen, which is now the standard treatment for carbon monoxide asphyxia, is also an effective preventive of postasphyxial pneumonia.

(*d*) In pneumonia it is the blocking of the lung airways, bronchi or bronchioli, by plugs of thick and sticky secretion which is the critical morbidic factor producing atelectasis and the conditions characteristic of an undrained infection.

2. The experiments here reported demonstrate these facts:

(*a*) Atelectasis that is induced experimentally in dogs by blocking a bronchus is quickly cleared up and the lung is redistended by the deep breathing induced by inhalation of carbon dioxide in proper dilution.

(*b*) Pneumonia that is induced in dogs by insufflation of a virulent culture of pneumococci is generally overcome, the lung is redistended and the animal is restored to health by inhalation of carbon dioxide sufficient to cause deep breathing and continued until the pneumonic area is cleared.

3. Success with this therapy for the relief of pneumonia in patients depends on administering the inhalation as early as possible. If medical pneumonia is thus treated early enough, it appears probable that the results may be as effective as those already attained in postoperative and postasphyxial pneumonia.

NOTE.—The second paper of this series will deal with the chemical and bactericidal effects of inhalation of carbon dioxide.

ATELECTASIS IN THE PATHOGENESIS OF ABSCESS OF THE LUNG

A STUDY OF SPONTANEOUS PULMONARY SUPPURATION IN THE ALBINO RAT *

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Although numerous observations have been made on pulmonary infection in the albino rat, definite knowledge concerning the etiologic agent and the factors in the pathogenesis of this disease is lacking. The lesions of the lungs vary greatly according to the stage and extent of the process, but the essential nature of the completely developed lesions is that of chronic pulmonary suppuration. The late stages of the disease are frequently misnamed "pneumonia," while the earlier manifestations of the condition are imperfectly understood. The purpose of the present communication is to present a series of observations which suggest that atelectasis subsequent to bronchial occlusion is a primary factor in the development of this disease.

The literature contains numerous assertions on the one hand that the lungs are sterile, and on the other hand that they frequently contain micro-organisms. Thomson and Hewlett [1] estimated that 1,500 organisms or more were taken into the air passages per hour in London and claimed that the ciliary action of the lining epithelium soon rids the inspired air of organisms. In addition to the action of the cilia, there is the important mechanism of phagocytosis in removing organisms from the respiratory tract.

The probable pathway of infection has been indicated in a study of the occurrence and source of the micro-organisms in the lungs of normal animals (Jones).[2] In not a single instance did all of the culture tubes inoculated with the lungs from guinea-pigs, rabbits and calves remain sterile, but in the mouse and the rat the proportion of positive

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* From the Department of Surgery and the Laboratory of Physiological Chemistry, Yale University.

* A preliminary report has been made in the Proceedings of the Society of Experimental Biology and Medicine **26**:723, 1929.

1. Thomson, St. C., and Hewlett, R. T.: Lancet **1**:86, 1896.
2. Jones, F. S.: J. Exper. Med. **32**:361, 1922.

cultures was much lower. It seemed probable to Jones that the high percentage of positive cultures in the herbivorous animals was due to the relatively larger number of organisms in the environmental atmosphere of these animals, probably originating from the hay and straw which form their diet. In further studies he was able to show that the number of positive cultures could be raised or lowered in proportion to the relative amount of dust in the atmosphere in which the animals were maintained. These observations have a practical bearing in the study of spontaneous and experimental pulmonary disease in animals. Although the organisms obtained were nonpathogenic, there is no reason to doubt that animal pathogens do gain an entrance in this manner.

The literature contains reports of numerous instances in which organisms have been isolated from the lungs of rats suffering from pulmonary infection. Klein [3] and Mitchell [4] have cultivated a granular gram-positive bacillus. This organism was named *Bacillus muris* by Klein. A streptothrix from the lungs of twenty rats was cultivated by Tunnicliff,[5] who also obtained a variety of other organisms (streptococci, staphylococci, pneumococci, diphtheroid bacilli, colon bacilli, etc.). Hoskins and Stout [6] obtained *Bacillus bronchisepticus* from the upper respiratory tract and lungs of rats suffering from pulmonary infection. Jones [7] isolated *B. actinoides* in eleven instances and *B. bronchisepticus* and a streptothrix from a few animals. The results of the bacterial cultures do not permit a definite conclusion as to the etiologic organism of pulmonary infection in white rats. In fact, they suggest that a variety of organisms may be involved.

The anatomic characteristics of the pulmonary lesions have been described by Hektoen [8] in the following words:

> Two main types of lesions may be distinguished. In one the affected tissue, most often part or parts of one or more lobes, is solid and red, usually with more or less well marked nodular areas of reddish-yellow or yellowish color; on the cut surface and in the microscopic sections such areas correspond with accumulations of exudate, which is mostly cellular, within the bronchial system, and in the earlier stages the consolidation of the tissue proper is due to cellular exudate in the alveoli with congestion associated with collapse. This is probably the more common lesion. In a few instances an entire lobe is found uniformly solid throughout, deeply congested and red or reddish-gray in color; rarely we have found more or less uniform congestion in one or more lobes with much mucus in the bronchi. In what may well be later stages of the bronchopneumonic process, the lungs are found "riddled with abscesses" with thick yellow pus; some

3. Klein, E.: Centralbl. f. Bakteriol. **33**:488, 1903.
4. Mitchell, O. W. H.: J. Infect. Dis. **10**:17, 1912.
5. Tunnicliff, R.: J. Infect. Dis. **19**:767, 1916.
6. Hoskins, H. P., and Stout, A. L.: J. Lab. & Clin. Med. **5**:307, 1919-1920.
7. Jones, F. S.: J. Exper. Med. **36**:329, 1922.
8. Hektoen, L.: Tr. Chicago Path. Soc. **10**:105, 1916.

of these appear to lie in bronchial dilatations, while others may have dense fibrous capsules.

In the second type of lesion districts of lung tissue, frequently with sharp but irregular margins, appear somewhat gelatinous, largely homogeneous, even translucent, light-gray or reddish-gray, though often with more opaque yellowish spots. The gelatinous appearance corresponds with mucoid degeneration of the bronchopneumonic exudate, and it may be associated with connective tissue proliferation, the mucoid material then usually appearing dense and inspissated.

These two main types of lesion may be present in the same lungs and in the same lobe, and individual lesions occur which appear to partake of the characteristics of each type. The difference between the two types would seem to depend on the predominance of suppuration in the one and of mucoid change in the other.

As a rule in well-marked cases the bronchi and the trachea contain much turbid, viscid mucus.

Special mention must be made of certain sharply defined, solid, deeply red areas, usually at the tips of lobes, which look very much like red infarcts, but are caused apparently by collapse of lung tissue due to occlusion of bronchi either by exudate or through fibrous obliteration. Then there are pure vesicle-like lesions, usually minute subpleural as well as deep, with clear, colorless mucoid contents, apparently formed by accumulation of mucus and mucoid material in bronchi and other spaces.

Usually the pleura is free and smooth; over large chronic abscesses there may be adhesions; occasionally scars are found and deposits of coal dust occur.

The studies mentioned in the foregoing paragraphs have made valuable contributions to the knowledge of pulmonary disease in the albino rat. The probable pathway of infection is suggested (Jones) [8] and the anatomic studies (Hektoen [8]) are complete, but the exact etiologic agent is obscure and the existing literature does not explain the pathogenesis of the disease. It is on the latter question, namely the mechanism of the condition, that our own observations and interpretation are significant.

EXPERIMENTAL WORK

Source of Material.—Most of the animals on which the present observations are based were used in an extensive dietary experiment. The others were obtained from miscellaneous sources. It is possible, therefore, to draw a correlation between the incidence and severity of the lesions and the level of the protein in the ration, the only variable in the experimental food. All the diets were adequate. Atelectasis and frank infection occurred irrespective of the diet fed.

Method.—The method of study has been to remove the intact trachea and lungs from a large number of rats and to make observations on the gross and microscopic anatomy. In certain instances the bronchi leading to affected areas were injected or dissected out, and in others corrosion specimens of the bronchial tree were prepared.

Observations.—The normal lung in the rat consists of a single large left lobe, an upper, middle and lower right lobe and an infracardiac

lobe. The latter lobe is a part of the right lung. In a few instances anomalous lobes were observed.

The lesions of the lungs vary greatly according to the stage and the extent of the process, but the essential nature of the completely developed disease is that of chronic abscesses of the lung. There are several main types of anatomic change representing different stages in the condition. The earliest and probably the commonest easily recognizable change is that of atelectasis. The affected part may be a small shrunken, solid, red collapsed area at the periphery of a lobe or a similar area involving an entire lobe or in some instances more than half of the entire area of the lung (figs. 1 and 2). If the process is

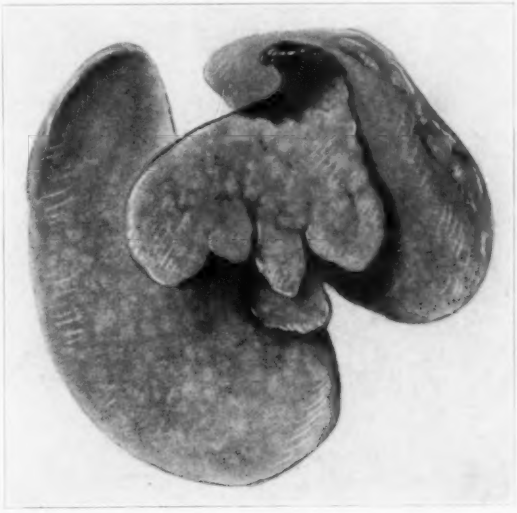

Fig. 1.—Obstructive atelectasis of the tip of the infracardiac lobe of the rat's lung. There is no evidence of infection. The remaining lobes are normal; × 2.

extensive, the uninvolved lobes are emphysematous. In this stage of the condition there is no gross or microscopic evidence of infection in the pulmonary parenchyma.

The second stage of the lesion shows areas with sharp irregular margins that appear as pearly-gray semitranslucent nodules at the edge of a lobe or situated within an atelectatic area. On cross-section these nodules contain a gelatinous mucoid substance. In some instances there is at this stage no evidence of abscess formation. The bronchi frequently contain accumulations of mucus in association with the two types of change described in the foregoing.

In the final stages of the disease, that of the well developed abscess, the lungs show multiple discrete or confluent yellow opaque nodules (fig. 3). On section, these areas contain thick yellow or greenish-yellow pus. In some instances the confluence of the individual abscesses produces a single large nodular mass occupying a major part of the thoracic cavity. A majority of the abcesses are situated within bronchial dilatations; others are apparently completely surrounded by dense fibrous capsules (fig. 4).

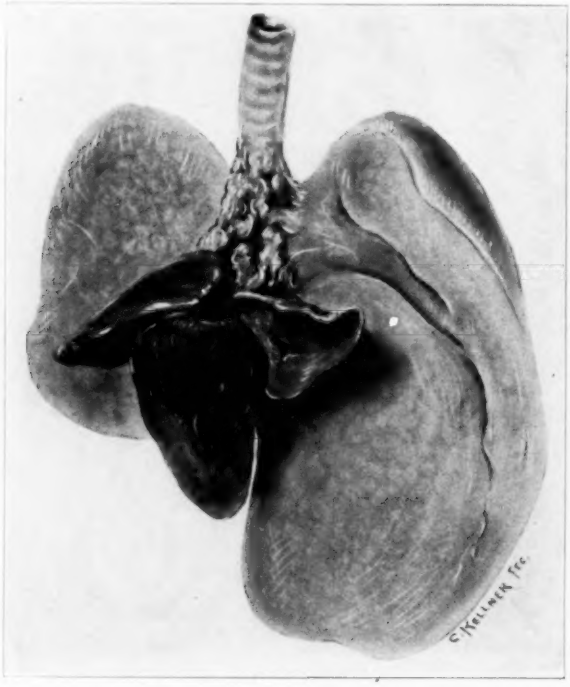

Fig. 2.—Obstructive atelectasis of the right middle, lower and infracardiac lobes. There is no evidence of infection. The right upper and the left lobes show a compensatory emphysema. Reduced from a magnification of $\times 2$.

The pleural cavity is rarely invaded but with the large confluent abscesses it is frequently partly obliterated by adhesions. In one instance, a purulent pleurisy and pericarditis were observed. In another animal there was a purulent pericarditis with marked dilatation of the pericardial cavity and thickening of the pericardium. There was no evidence of infection in any of the other organs of the rats studied.

By injection and dissection of the bronchial tree, points of occlusion of the bronchi leading to the atelectatic areas have been demonstrated (fig. 5). In this manner mucous plugs completely occluding the bronchial lumina were observed just proximal to the collapsed areas. In some instances, the minute size of the bronchi precluded the demonstration of such plugs, although there is no doubt concerning the obstructive nature of the atelectasis.

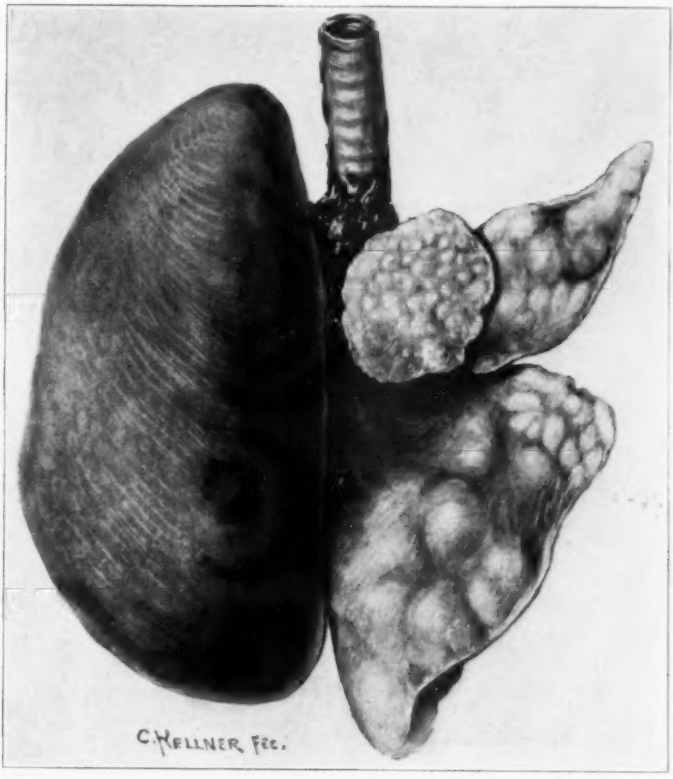

Fig. 3.—The right upper lobe shows multiple small abscesses superimposed on an atelectasis. The right middle and lower lobes show multiple larger abscesses. These lobes are not collapsed. The left lobe is normal. Reduced from a magnification of $\times 2$.

A detailed study of microscopic sections confirmed the foregoing observations on the gross anatomy. In the early atelectatic stage of the disease the pulmonary parenchyma is collapsed (fig. 6). There is no alveolar or bronchial exudate. In an apparently later stage, accumu-

lations of an amorphous noncellular material (mucus) are observed within dilated bronchi, and in still later stages a thick purulent exudate, containing a variable quantity of mucus. The sections also show that many of the abscesses are within bronchiectatic cavities; others are encapsulated by a dense fibrin band. In some sections the bronchiectatic abscess cavities are lined by normal bronchial columnar epithelium; in others the lining cells are of the pavement type, and in some areas no epithelial cells are observed.

The exudate within the lung tissue is largely peribronchial in distribution. In fact, there is little if any evidence of a "pneumonia" except

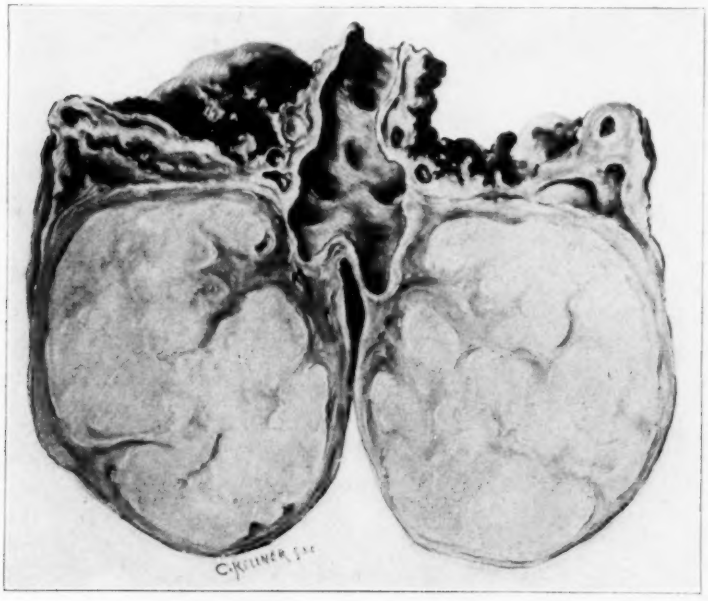

Fig. 4.—The drawing shows a large bronchiectatic abscess; × 2.

as a result of direct extension of the infection to areas immediately contiguous to abscesses. In a few instances, microscopic sections showed a purulent exudate within groups of alveoli scattered throughout an atelectatic lobe.

The well recognized fact that pulmonary suppuration is less common in active than in inactive animals is in accord with our hypothesis, as the more active rat is less likely to develop bronchial obstruction and subsequent atelectasis. The relative infrequency of pulmonary disease in active rats is in accord with experience in this and in other laboratories. Furthermore, this suggests that the infection can be prevented

by periodic administration of air mixtures rich in carbon dioxide. The hyperventilation of the lungs, resulting from such therapy, would probably prevent the accumulation of mucus in quantities sufficient to occlude a bronchus.

COMMENT

The interpretation of our observations is dependent on an understanding of the pathogenesis of atelectasis and the significance of this condition in relation to the development of pulmonary infection.

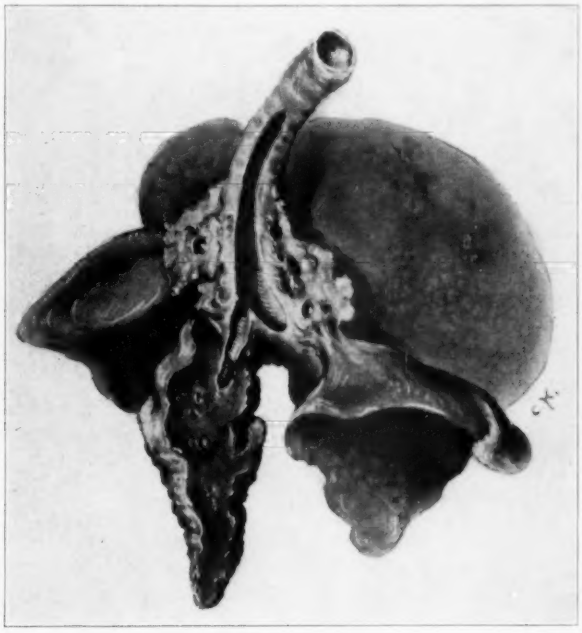

Fig. 5.—Obstructive atelectasis of the right lower lobe. The bronchus leading to this lobe is completely occluded by a plug of blood-stained mucus; × 2.

Although the literature on this subject extends back into the first half of the nineteenth century, a widespread appreciation of the causative factors is recent and even now is not sufficiently understood. General interest in the subject has been aroused by numerous reports on the subject of "massive collapse of the lungs," and as a result of these studies the question is one of considerable clinical import. In addition to recent reports, this revival of interest in atelectasis has brought to light some remarkable observations by earlier investigators. The most notable of

these is probably that of Lichtheim [9] who, in 1879, clearly demonstrated that the complete obstruction of a bronchus and subsequent absorption of air leads to collapse of the lung peripheral to the point of obstruction. In a recent report, Coryllos and Birnbaum [10] made an exhaustive review of the literature and showed that there are two causes of collapse; the complete occlusion of a bronchus and compression of the lung. On the basis of this knowledge patients with postoperative massive collapse are being treated successfully by various procedures directed toward relief

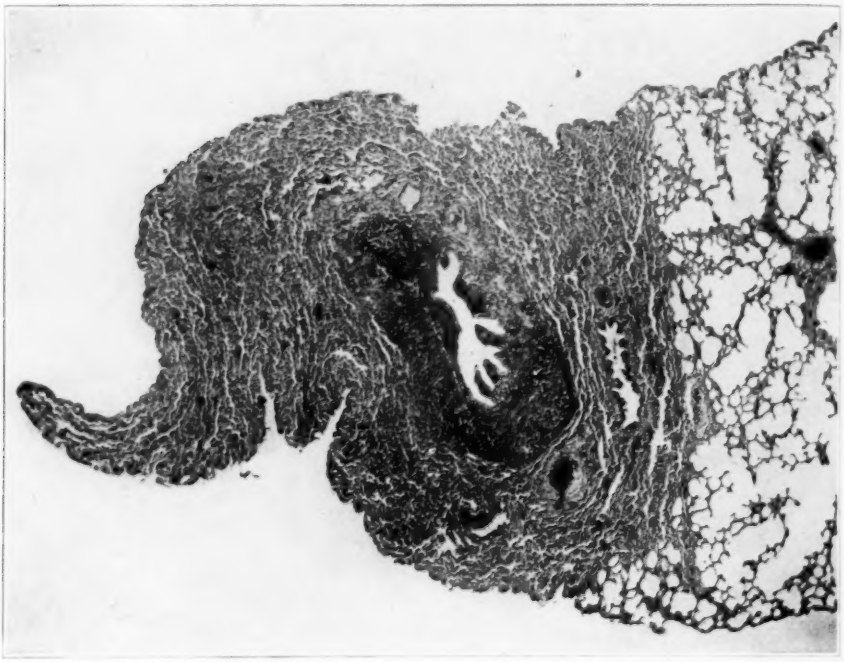

Fig. 6.—Obstructive atelectasis of the tip of the infracardiac lobe. There is no evidence of infection in either the collapsed or the normal portion of the section. Compare with figure 1.

of the obstructed bronchus. Coryllos and Birnbaum have presented additional evidence suggesting that lobar pneumonia may be the result of a similar phenomenon. Although the facts are not yet entirely clear, there is little doubt that obstructive collapse or atelectasis is an important factor in the development of certain pulmonary lesions in human beings.

9. Lichtheim, L.: Arch. f. exper. Path. u. Pharmakol. **10**:54, 1879.

10. Coryllos, P. N., and Birnbaum, G. L.: Obstructive Massive Atelectasis of the Lung, Arch. Surg. **16**:501 (Feb.) 1928.

In our own studies we have been particularly impressed with the frequency of the occurrence of atelectasis in white rats. This has been observed many times in animals apparently normal and showing no evidence of pulmonary suppuration. The areas of atelectasis have varied in size from the collapse of a minute portion at the tip of a lobe to a massive collapse of one entire side and the infracardiac lobe. In many instances there was no associated gross or microscopic evidence of infection. In others, smaller or larger abscesses were seen within the collapsed portions of the lungs. These observations lead us to the conclusion that atelectasis is a primary factor in the development of pulmonary infection in the white rat.

To substantiate this hypothesis it is necessary to show that obstructive atelectasis occurs in white rats showing no evidence of pulmonary infection and that organisms already present may cause abscesses in the collapsed lobes. On the latter point it is well known that obstruction to any part is an important factor in the localization of an infectious process. In many instances we have demonstrated occlusive mucous plugs in the bronchi leading to such collapsed lobes. The occurrence of excessive mucus in the bronchi of white rats has been frequently observed (Mitchell [4] and Hektoen [7]). The points of occlusion have been demonstrated by injection of air and fluid into the trachea and by careful dissection of the bronchi leading to collapsed lobes. The objection that the occlusion may develop as the result of infection can be readily answered by our frequent observations of obstructive atelectasis in animals showing no evidence of pulmonary infection. In fact this is frequently found in animals apparently in perfect condition.

SUMMARY

Obstructive atelectasis is a common observation in otherwise healthy albino rats. The obstruction is frequently the result of the accumulation of mucus in the form of a plug completely occluding the bronchial lumen. Micro-organisms may be frequently obtained from the lungs of healthy animals (Jones [2]). On the basis of these observations, it is probable that the sequence of events in the pathogenesis of pulmonary disease in the white rat is the entrance of organisms into the lung, an obstructive atelectasis followed by the growth of organisms distal to the point of occlusion and the development of pulmonary suppuration. The established suppurative process may extend to other parts of the lung by a repetition of these changes or by direct extension to adjacent structures.

THE TREATMENT OF ACUTE EPIDEMIC POLIOMYELITIS BY THE INTRATHECAL ADMINISTRATION OF EPHEDRINE *

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Acute epidemic poliomyelitis is a systemic infection in which the most important lesions occur in the central nervous system. Unless the disease process is checked, the meningeal irritation is followed in a short time by manifestations of involvement of the nerve tissue proper. The initial toxic reaction in the cord or brain stem is a hyperemia and edema, resulting in a local increase in pressure. At the site of the local increase in pressure the smaller blood vessels are compressed, and the part of the cord supplied by these vessels becomes anemic. A deficient blood supply means a deficient oxygen supply. The injurious effects of anoxemia take place rapidly in the nerve tissue.[1] If the anoxemia is not relieved, injury to the nerve cells will result. In experimentally produced poliomyelitis in monkeys, Flexner and Lewis [2] found that "the chief lesion (in the cord) consisted of edema, injection of the vessels and punctiform and larger (pinhead) hemorrhages. The lesions tend to be most marked in regions of the spinal cord corresponding with the paralyzed groups of muscles. The congestion is more apparent than the hemorrhages." Peabody, Draper and Dochez,[3] in their pathologic studies of human cases, found that "It is quite impossible to exclude the fact that the virus may exert some directly toxic action on these (nerve) cells, but in many ways, the clinical and anatomical pictures are readily explained by the pressure of the circulatory disturbance and of the exudate. . . . The damaging effects can be assumed to result in

* Submitted for publication, May 15, 1929.

* From the services of Dr. Philip Moen Stimson and Dr. Henry W. Berg, Willard Parker Hospital.

1. Gomez, L., and Pike, F. H.: The Histological Changes in Nerve Cells Due to Total Temporary Anemia of the Central Nervous System, J. Exper. Med. **11**:257, 1909.

2. Flexner, S., and Lewis, P. A.: Experimental Epidemic Poliomyelitis in Monkeys, J. Exper. Med. **12**:236, 1910.

3. Peabody, F. W.; Draper, G., and Dochez, A. R.: A Clinical Study of Acute Poliomyelitis, Monograph of The Rockefeller Institute for Medical Research, IV, 1912.

part from the direct pressure on the nerve cells of hemorrhage, edema and exudate. There is also the additional factor of anemia following the constriction of the blood vessels by the same mechanism. On account of this pressure and anemia the nerve cells degenerate. If the hemorrhages and exudate are absorbed soon enough the cells may recover their function. If, on the other hand, the anemia and pressure have been prolonged or excessive, the nerve cells go on to complete necrosis. . . . It is noteworthy, however, that it is often extremely difficult to reconcile the clinical symptoms which are referable to pontine lesions with the actual autopsy findings. Cases which have bulbar paralysis during life may fail to show adequate anatomical lesions to account for death and other cases which have clinical evidence of spinal involvement may show changes only through the pons and medulla." Meltzer,[4] commenting on these observations, stated that "It is possible that while the victim is still alive and the circulation active, hyperemia and edema are much more extensive than after the heart has stopped beating for a time."

In addition to the deleterious mechanical effect of the reaction in the central nervous system, some investigators[5] feel that there is a direct toxic action on the nerve cells. Even if a direct toxic action does occur, it is important to maintain the resistance of the nerve cells at the highest level possible. The congestion and edema in the surrounding tissue which interfere with the nutrition and metabolism of the nerve cells are of great importance in the production of the paralyses.

If the diagnosis of poliomyelitis is made in the preparalytic stage, we feel that the patient should be given convalescent serum. Shortly after the first paralysis appears, serotherapy fails to influence the course of the disease.[6] At this stage, and later, treatment must be instituted to relieve the damaging local reaction in the central nervous system. To accomplish this, it is necessary to diminish the hyperemia and edema.

In the past, several methods have been tried, but without success. The injection of hypertonic solutions by vein or by rectum has been of uncertain value. Repeated lumbar puncture has not proved effective.[7] In 1916, Meltzer [4] tried epinephrine in a series of cases. The mortality

4. Meltzer, S. J.: The Treatment of Acute Poliomyelitis, New York M. J. **104**:337 (Aug. 16) 1916.

5. Howe, H. S.: The Pathology of Human and Experimental Poliomyelitis, J. Nerv. & Ment. Dis. **50**:409 (Nov.) 1919. Mönckeberg: Anatomischer Befund eines Falles von Landryschen Symptomkomplex, München. med. Wchnschr. **45**:1958 (Nov. 10) 1903.

6. Mönckeberg: The Epidemic of Poliomyelitis in New York in 1916, Monograph of the Department of Health, New York City, 254, 1917. Aycock, W. L., and Amoss, H. L.: The Serum Treatment of Experimental Poliomyelitis, Bull. Johns Hopkins Hosp. **34**:361 (Nov.) 1923. Flexner, S., and Lewis, P. A.: Epidemic Poliomyelitis, J. A. M. A. **57**:1685 (Nov. 18) 1911.

7. Mönckeberg (footnote 6, first reference).

in his cases in which treatment was given was higher than in his control group.[7] However, an important observation was made by Hoyne and Cepelka [8] in cases in which epinephrine was given intrathecally. They noticed that in several instances the paralysis of a limb was temporarily lessened after treatment. In other words, the motor nerve cells regained their function temporarily as a result of the local astringent action of the epinephrine. This drug, however, is not suitable for the maintenance of a vasoconstrictor and astringent action. Its effects are rapid and intense, but of short duration. Moreover, a secondary vasodilatation sometimes occurs which may be harmful.

In 1924, Chen and Schmidt [9] brought ephedrine to the attention of the medical profession. In contrast to epinephrine, ephedrine has a less intense and a more prolonged vasoconstrictor action and is not followed by a secondary vasodilatation.[10] This makes it especially useful for local application in poliomyelitis.

The cases reported in this paper are those of patients with bulbar lesions admitted to the Willard Parker Hospital during August and September, 1928. As in other diseases, the percentage of very sick patients was higher in the hospital than in the city at large. On admission to the hospital, all patients were classified as severely ill or moderately ill. Moderately ill patients were those without prostration, whose bulbar lesions were of long standing without any evidence of extension. On admission some had nasal regurgitation and others, facial paralysis. In these cases, the prognosis for life was considered good. On the other hand, the majority of patients were very sick, were prostrated, had extensive bulbar involvement and gave the impression that their chances for recovery were small. These were classified as severely ill. We realize that without more numerous specific points on which to base a prognosis, such a classification may be fallacious. However, the patients we considered as moderately ill all survived, whereas among those considered severely ill the mortality was high, as will be shown later.

TECHNIC

Lumbar puncture was done on admission for diagnostic purposes in all cases. If the spinal fluid was under normal or slightly increased

8. Hoyne, A. L., and Cepelka, F. P.: Poliomyelitis, J. A. M. A. **67**:666 (Aug. 26) 1916.

9. Chen, K. K., and Schmidt, C. F.: The Action of Ephedrine, J. Pharmacol. & Exper. Therap. **24**:339 (Dec.) 1924.

10. Rudolph, R. D., and Graham, J. D.: Notes on the Sulphate of Ephedrine, Am. J. M. Sc. **173**:399 (Jan.) 1927. Kreitmar, H.: Pharmakologische Wirkung des Ephedrins, Arch. f. exper. Path. u. Pharmakol. **120**:189, 1927 King, T., and Pak, C.: Ephedrine on the Nasal Mucous Membrane, Chinese J. Physiol. **1**:445 (Nov.) 1927.

pressure, from 4 to 6 cc. was removed for laboratory examination. If the pressure was greatly increased, spinal fluid was removed until the pressure was approximately normal. When ephedrine was administered, the last 2 to 4 cc. of spinal fluid was retained in the gravity tube. From 40 to 60 mg. of an ephedrine salt in 1 cc. of sterile water was added to spinal fluid and permitted to gravitate into the spinal canal. The average dilution was 50 mg. of drug in 5 cc. of fluid, or a concentration of about 1 per cent. In severe cases, it may be advisable to give two or more daily injections during the first few days.

Ephedrine was given intrathecally in ten cases during August and September. On admission, the patients in these cases were classified as severely ill with a poor prognosis for life. Five of the ten died, a mortality of 50 per cent. The first death occurred in the case of a young man who had a palatal paralysis of four days' duration. At the time of admission, he was apprehensive and restless; his temperature was 100.4 F., the pulse rate 110 and respirations, 22. There was involvement of the upper cervical nerves and the third, fourth, ninth and eleventh

Bulbar and Bulbospinal Cases of Poliomyelitis in the Willard Parker Hospital During August and September, 1928

	Total No. of Patients	Moderate	Severe	Total No. of Deaths	Mortality, per Cent in Severe Cases
Untreated	19	7	12	9	75
Treated	10	0	10	5	50

cranial nerves. His condition grew rapidly worse, and he died twenty-four hours after admission. Another death was that of a boy, aged 8 years, who had a widespread bulbar and spinal involvement. Two injections of ephedrine were followed by an improvement, and no more was given. Five days later, the boy developed respiratory paralysis and died. In two other patients the drug was given in extremis; one died in one hour, the other in three hours. The failure of a therapeutic procedure under such conditions is not in itself an indication of inefficacy. Recovery or death is a definite but not the only criterion by which a therapeutic measure may be judged. It was our impression that in several instances improvement was more rapid in cases in which treatment was given than in the control cases.

CONTROL CASES

As a control group, we used all the other patients with bulbar poliomyelitis admitted to the hospital during August and September. On admission, the cases were classified as moderate or severe on the basis previously described. One patient admitted in September is not included because autopsy revealed a complicating bronchopneumonia. We did

not feel certain that death was due directly to poliomyelitis. There was a total of nineteen other cases in this group, seven moderate and twelve severe. Nine of the twelve patients with severe cases died, a mortality of 75 per cent, as compared with a mortality of 50 per cent among those treated with ephedrine. The criticism may be made that some of the bulbar cases in which treatment was not given were not included in the control group because they were classified as moderate. The accuracy of the classification has already been alluded to. However, we can take the total number of bulbar cases in which treatment was not given, including both moderate and severe, and compare the mortality percentage in the two groups. There was a total of nineteen moderate and severe cases in which treatment was not given, with nine deaths, a mortality of 47.4 per cent, which is little less than the mortality of 50 per cent in the severe cases, in which treatment was given, as shown in the accompanying table.

REPORT OF CASES

The following are abstracts of two cases in which ephedrine was used:

CASE 1.—H. L., a boy, aged 3½ years, was admitted to the Willard Parker Hospital on Sept. 18, 1928. His present illness began seven days prior to admission with fever and malaise. Following this, there gradually developed a nasal tone to the voice, regurgitation of food through the nose and inability to swallow.

On physical examination, the child was extremely prostrated, well developed and well nourished. The pharynx filled up with saliva which the child seemed unable to swallow or expectorate. There was left facial paralysis, paralysis of the left half of the soft palate, deviation of the tongue to the left and marked weakness of the muscles of the neck and back. The patellar reflexes were greatly diminished. The heart and lungs were normal. The temperature was 102.4 F., the pulse rate 138, and respirations 38. The spinal fluid on admission was clear and under approximately normal pressure. There was a moderate mononuclear pleocytosis; the albumin, globulin and sugar content were normal. Forty milligrams of ephedrine was given intrathecally. There was no obvious reaction to the drug.

On September 19, the child was restless and irrational, and the general condition was poor. In addition to the condition found on admission, there were nystagmus and paralysis of the right half of the palate. The heart and lungs were normal. Frequent aspiration of the fluid accumulated in the pharynx was necessary. The patient regurgitated feedings given by mouth. The temperature was 102.4 F., the pulse rate 124, and the respiratory rate 30. Fluids were given rectally and intraperitoneally.

On September 20, the child was restless but less irrational, and the general condition was poor. The temperature was 102 F., the pulse rate 116, and respirations 30. Ten cubic centimeters of clear spinal fluid under slightly increased pressure was removed by lumbar puncture. Forty-five milligrams of ephedrine sulphate was given intrathecally.

On September 21, the general condition was poor but was a little better than on the previous day. Nystagmus was no longer present. The muscles of the neck and back were stronger. The palatal, pharangeal and facial paralyses

persisted. The patellar reflexes were stronger. The temperature was 101.2 F., the pulse rate 124, and respirations 28. Spinal fluid obtained by lumbar puncture was clear and under normal pressure. Forty-five milligrams of ephedrine sulphate was given intrathecally.

On September 23, the patient was brighter. The temperature and pulse rate were normal. There was no change in the paralyses.

On September 24, the general condition was improved. The temperature and pulse rate were normal. The rectal and intraperitoneal administration of fluids was discontinued because the patient retained feedings by gavage.

On the 25th, the facial paralysis had diminished, but the palatal paralysis persisted. Gavage was still necessary.

On the 27th, the patient developed otitis media on the right side; the temperature was 102.8 F.

On the 29th, he was able to stand up unassisted. The palatal and pharangeal paralyses persisted. There was a purulent discharge from the right ear.

On October 4, the patient was able to swallow, and gavage was discontinued. There was a slight discharge from the right ear. The temperature and pulse rate were normal.

On October 9, the general condition was good. The patient swallowed with greater ease.

On October 16, the patient was ready to be discharged but had developed impetigo contagiosa. On October 26, he was discharged. There were slight residual palatal and facial paralyses.

On November 14, a follow-up note stated that the child had been well since discharge. His general condition was good. There was no nasal regurgitation. Slight weakness of the facial and palatal muscles on the left side persisted. The other muscles were normal.

Case 2.—P. C., a boy, aged 7 years, was admitted to the Willard Parker Hospital on Sept. 15, 1928. Two days prior to admission, he complained of headache and pain in the nape of the neck. The following day he vomited and developed difficulty in swallowing and nasal regurgitation.

On physical examination, the boy was fairly well developed, acutely ill and prostrated. There was slight rigidity of the neck, a lower left facial palsy, slight ptosis of the left upper eyelid, deviation of the tongue to the left and bilateral paralysis of the palate. Frothy secretion accumulated in the pharynx. There was a nasal tone to the voice and great difficulty in swallowing. The muscles of the neck and back were weak. The extremities, heart and lungs were normal. The temperature was 104 F., the pulse rate 136, and the respiratory rate 24. The spinal fluid obtained by lumbar puncture was under approximately normal pressure and contained 15 cells per cubic millimeter, 90 per cent of which were mononuclear. Forty milligrams of ephedrine hydrochloride was given intrathecally. There was no obvious reaction to the drug.

On September 16, the general condition was poor. The patient was restless and had developed incontinence of urine. The pharynx filled up rapidly with saliva. The temperature was 102.4 F., the pulse rate 138, and the respiratory rate 32. Forty milligrams of ephedrine hydrochloride was given intrathecally.

On September 17, the general condition was poor. The patient was irritable and was fed with difficulty. Gavage was discontinued, and fluids were given rectally and intraperitoneally. Forty milligrams of ephedrine hydrochloride was given intrathecally.

On September 18, the general condition was a little better. There was no spread of the paralyses; urine was voided normally. The temperature was 100.2 F. Forty-five milligrams of ephedrine sulphate was given intrathecally.

On September 19, the condition was unchanged. Forty-five milligrams of ephedrine sulphate was given intrathecally.

On September 20, 45 mg. of ephedrine sulphate was given intrathecally.

On Sept. 21, the general condition was better. The patient swallowed small quantities of fluids, but with great difficulty. There was a slight spasticity of the arms and legs. Forty-five milligrams of ephedrine sulphate was given intrathecally.

On the 22nd, the patient was able to swallow a little better. The extremities were normal.

On the 23rd, the general condition was much improved. There was still paralysis of the muscles of the left eyelid, face, tongue, both sides of the palate and the pharynx. The muscles of the neck and back were stronger. The temperature was normal.

On September 26, there was an improvement in speech. The patient swallowed more easily, occasionally regurgitating through the nose.

On October 7, the patient's general condition was good. His speech was greatly improved. He was able to hold up his head unassisted.

On October 11, he was discharged, much improved. There was residual weakness of the muscles of the left eyelid, the left side of the face and the left half of the palate. The muscles of the neck and back were normal, except the left sternocleidomastoid which was a little weak. The extremities were normal.

On November 11, a follow-up note stated that the patient experienced a little difficulty in swallowing for a time after discharge, but there was no regurgitation. There was a nasal tone to the voice. His general condition was good. The residual muscle weaknesses are the same as at the time of discharge.

COMMENT

In poliomyelitis, injurious hyperemia and edema in the cord and brain stem occur. A local increase in pressure and an anoxemia result, which impair the function and injure the nerve cells. The rapid relief of this local reaction is of paramount importance. The direct application of ephedrine to the lesion by intrathecal administration seems, therefore, a rational method of treatment.

In a disease with as varied a course as has poliomyelitis, the evaluation of a therapeutic measure is difficult. In our small series including only bulbar cases in which the prognosis for life was poor, the mortality was 50 per cent. In a control group of patients with apparently similar cases admitted to the hospital during the same time interval, the mortality was 75 per cent.

We feel that our patients were benefited and the mortality reduced by the use of ephedrine. In interepidemic years, the material available in one hospital is small. For this reason, we present our first series of cases as a preliminary report so that the treatment with ephedrine may be tried in other hospitals.

55 Central Park West.

THE EFFECT OF HYPNOSIS ON BASAL METABOLISM *

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In the past, work has been done concerning the effect of mental activity on basal metabolism. Some investigators, Speck,[1] Loewy,[2] Johansson [3] and Benedict and Carpenter,[4] found a slight increase in the metabolic rate during mental activity. Grafe,[5] in his monograph, also concluded that mental effort probably has an influence on metabolism.

The effects of strong emotional reactions on basal metabolism in the waking and in the hypnotic states have also been studied. Grafe [6] mentioned a metabolism experiment in which intense sorrow increased the metabolic rate. Du Bois [7] cited a similar observation brought on by anger. Like observations have been made by Hafkesbring and Collett,[8] who noticed that harsh or sudden noises had a tendency to increase metabolism. Landis [9] noted that strong emotions usually cause an increase in the metabolic rate. In his experiments, anticipation of a strong electrical stimulation raised the metabolism in the three persons tested, 6, 17 and 37 per cent.

In making tests on psychasthenic war veterans, Ziegler and Levine [10] found a marked rise in metabolism in eleven cases; in three, there was

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* From the Psychiatric Service of the Worcester State Hospital.

1. Speck: Untersuchungen über die Beziehungen der geistigen Thätigkeit zum Stoffwechsel, Arch. f. exper. Path. u. Pharmakol. **15**:81, 1882.

2. Loewy: Ueber den Einfluss einiger Schlafmittel auf die Erregbarkeit des Athemcentrums nebst Beobachtungen über die Intensität des Gaswechsels im Schlafe beim menschen, Berl. klin. Wchnschr. **28**:434, 1891.

3. Johansson, J. E.: Ueber die Tagesschwankungen des Stoffwechsels und der Körpertemperatur in nüchternen zustande und vollständiger Muskelruhe, Skandin. Arch. f. Physiol. **8**:105, 1898.

4. Benedict and Carpenter: United States Department of Agriculture Office of Experiment Stations, 1909, Bull. 208.

5. Grafe, E.: Ergebn. d. Physiol. **21**:499 (part II) 1923; Klin. Wchnschr. **2**:1005, 1923.

6. Grafe and Traumann: Zur frage des Einfluss psychischer Depressionen und der Vorstellung schwerer Muskelarbeit auf den Stoffwechsel (Untersuchungen in der Hypnose), Ztschr. f. d. ges. Neurol. u. Psychiat. **62**:237, 1920.

7. Du Bois: Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1927, p. 411.

8. Hafkesbring, R., and Collett, M. E.: Day to Day Variations in Basal Metabolism of Women, Am. J. Physiol. **70**:73, 1924.

9. Landis, C.: Studies on Emotional Reactions: IV. Metabolic Rate, Am. J. Physiol. **74**:188, 1925.

10. Ziegler, L. H., and Levine, B. S.: The Influence of Emotional Reactions on Basal Metabolism, Am. J. M. Sc. **169**:68, 1925.

a fall, and in one, no change. They produced emotional situations by having the veterans, during the breathing period, think of their disagreeable war experiences.

Comparatively speaking, little work has been done concerning the effect of strong emotions, suggested by means of hypnosis, on basal metabolism. In all probability, Grafe has done more work in this field than any one else. In 1920, he and Traumann [6] studied two subjects under hypnosis. One subject, under the hypnotic suggestion of depression, showed an increase of from 6 to 12 per cent in the metabolic rate, while the other manifested no appreciable change. Later, Grafe and Mayer [11] experimented on ten more subjects. The basal metabolism of each subject was determined under deep hypnosis, and then various emotional stimuli were given each subject while under hypnosis. The basal metabolism was determined under these conditions. Dreadful calamities, such as the amputation of arms, death of relatives and fights with cannibals, were suggested. In six subjects a distinct rise ranging from 8 to 25 per cent was found; in one case, only a slight rise, and in another, no change. Two subjects received pleasant suggestions; here only a slight rise in the metabolic rate was noted.

Grafe concluded that emotions may cause a distinct increase in metabolism and that emotions which produce sorrow increase the metabolism more than the ones that cause joy.

As far as I can discover, there has been no attempt, at least on a large scale, to determine what effect hypnosis, per se, has on basal metabolism. In this work the purpose was to obtain, by hypnosis, as complete a mental and physical relaxation as possible and then determine what effect, if any, this condition had on basal metabolism. Instead of stimulating mental activity, as did other investigators, suggestions were given to produce as complete a mental passivity as could be brought about.

Eighteen young normal men and women—mostly students of nursing and occupational therapy—volunteered for this work. None of them presented any gross physical or mental abnormalities.

METHODS

The procedure varied in different cases. In some, the subjects were first placed under hypnosis. Only those who went under deeply and who experienced no subjective mental or physical discomfort were selected to continue with the experiment. A test of the basal metabolism was made on each in the waking state under the usual conditions. Readings of the blood pressure, pulse rate and respiration were made. Blood was taken for a complete blood count and chemical analysis. That day, or a few days later, and in exceptional cases several days later, the same

11. Grafe, E., and Mayer, L.: Ueber den Einfluss der Affekte auf den Gesamtstoffwechsel, Ztschr. f. d. ges. Neurol. u. Psychiat. **86**:247, 1923.

procedure was repeated, only this time under deep hypnosis. Suggestions to induce as complete a mental and physical relaxation as possible were repeatedly given under hypnosis, before the actual taking of the basal metabolism. It was noticed that whenever suggestions were made repeatedly, even during the breathing period of the basal metabolism procedure, there was a tendency for the basal metabolic rates to be

TABLE 1.—*Basal Metabolism, Pulse, Respiration and Blood Pressure Readings in the Waking State and Under Hypnosis* *

Case	Age	Sex	State	Basal Metabolism, per Cent	Pulse Rate	Respirations	Blood Pressure
1	19	M	W	+ 6.5	75	15	110/76
			H	— 1.8	67	9	98/50
2	20	M	W	+ 2.5	62	12	92/48
			H	— 1.5	62	13	96/66
3	22	F	W	— 0.5	60	16	110/80
			H	— 2.5	66	16	104/74
4	22	F	W	— 4.0	70	14	104/64
			H	—11.0	60	15	100/74
5	21	F	W	— 4.7	64	16	104/60
			H	— 9.0	62	14	110/74
6	19	M	W	— 5.3	52	14	98/50
			H	—10.3	52	16	106/68
7	22	F	W	— 6.5	64	12	92/54
			H	— 9.5	62	11	92/54
8	24	M	W	— 7.0	66	14	108/72
			H	— 9.4	70	9	100/52
9	34	F	W	— 8.1	60	16	102/68
			H	— 8.7	62	12	102/74
10	22	F	W	— 8.1	64	18	110/68
			H	— 9.0	66	12	104/68
11	26	F	W	— 8.5	68	20	108/64
			H	—14.4	64	20	100/72
12	20	F	W	— 9.2	88	16	104/78
			H	—14.0	80	15	108/72
13	22	F	W	—10.3	64	15	108/58
			H	—11.7	54	15	94/64
14	20	F	W	—11.9	66	12	102/68
			H	—13.0	60	8	110/88
15	20	F	W	—12.8	76	14	96/64
			H	—16.1	78	12	112/80
16	20	F	W	—14.0	60	14	90/30
			H	—21.0	62	14	98/68
17	20	F	W	—14.5	70	15	106/66
			H	—20.0	72	12	104/60
18	25	F	W	—15.5	68	20	94/50
			H	—19.0	64	12	94/38

* The physical observations, the temperature and the urinalyses were all essentially normal. The readings under pulse and respiration are the average.
W indicates the waking state; H, the hypnotic state.

higher than the ones in which the suggestions were given only at the start of the experiment.

In other cases, the procedure varied in that the subject had the normal basal metabolic rate taken before any attempts were made to see whether or not he was a good hypnotic subject. Later the basal metabolism was done with the subject under hypnosis.

In a few cases, the basal metabolic rates were taken first with the subjects under hypnosis and then with them in the waking state.

It was observed that the variation in the order of procedure had no appreciable effect on the results.

Whenever a subject did not attain to an apparently complete mental and physical passivity under hypnosis, the tests were repeated. All tests

TABLE 2.—*Blood Chemistry and Blood Count Readings as Found in the Waking State and Under Hypnosis* *

Case	State	Nonprotein Nitrogen	Urea	Uric Acid	Sugar	Creatinine	Hemoglobin, per Cent	Red Blood Cells	White Blood Cells	Polymorphonucleears, per Cent	Lymphocytes	Eosinophils	Transitionals	Basophils
1	W	31	29	3.4	100	1.1	80	460	600	56	40	2	2	0
	H	33	14	2.9	80	1.7	80	400	670	54	42	1	1	0
2	W	29	12	3.8	111	1.5	90	465	740	56	41	2	1	0
	H	37	14	4.4	83	1.5	85	400	645	59	38	1	2	0
3	W	27	12	3.2	100	1.4	80	394	1,375	63	33	1	0	0
	H	27	11	2.9	98	1.4	80	388	1,240	67	32	0	1	0
4	W	31	15	4.3	83	1.4	80	492	705	47	52	1	0	0
	H	..	..	...	..	...	80	460	790	83	16	1	0	0
5	W	26.5	11	4.3	114	1.5	80	485	750	58	39	1	1	1
	H	..	..	...	....	...	80	460	755	61	37	1	0	1
6	W	32	16	4.5	105	1.5	95	395	1,000	69	31	0	0	0
	H	38	18	4.4	105	1.5	95	487	490	48	50	0	2	0
7	W	31	14	3.3	98	1.4	85	433	700	64	34	1	1	0
	H	30	13.4	3.2	91	1.4	85	443	915	69	27	0	3	1
8	W	30	12	3.1	104	1.3	80	490	830	53	43	2	2	1
	H	29	12	3.9	100	...	85	497	805	56	44	0	0	0
9	W	38	14	2.3	93	1.3	80	415	655	73	23	0	4	0
	H	34	11	2.3	111	1.1	80	408	675	65	33	0	2	0
10	W	30	13	4.7	125	1.4	80	512	785	49	48	0	3	0
	H	36	20	4.0	121	...	95	475	990	66	33	0	1	0
11	W	35	14	3.3	105	1.8	80	424	495	65	35	0	0	0
	H	32	13.4	3.4	100	1.6	85	390	655	46	51	1	1	1
12	W	25	11	3.4	117	1.1	85	497	1,035	62	33	2	1	1
	H	25	11	3.5	113	1.1	80	490	625	73	26	1	0	0
13	W	38	15	3.6	108	1.2	80	520	960	77	20	0	3	0
	H	37	12	3.4	107	1.1	80	480	430	33	64	1	0	2
14	W	26	13	4.4	83	1.1	85	434	500	50	50	0	0	0
	H	24	19	4.4	123	1.1	80	469	590	48	49	1	0	1
15	W	32	12	2.4	91	1.4	80	478	810	59	37	0	3	0
	H	25	12	2.4	100	1.4	85	582	795	70	25	3	2	0
16	W	37	19	3.2	83	1.4	85	492	825	55	41	1	3	0
	H	40	16	3.8	100	1.1	85	425	615	56	41	2	2	0
17	W	29	15	2.9	105	1.7	85	408	665	59	37	0	4	0
	H	37	15	3.1	108	1.4	85	408	720	67	33	0	0	0
18	W	33	15	2.7	87	1.7	80	402	845	57	39	2	2	0
	H	32	14	3.1	83	1.6	80	494	880	72	27	0	1	0

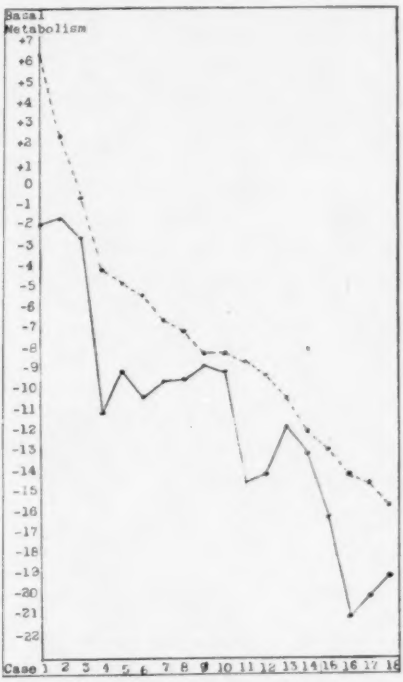
* For true reading under red blood count, multiply the figure given by 10,000. To obtain the correct white blood cells, multiply by 10.

in which the subject reported more than minimum mental activity were disregarded.

The basal metabolic readings were obtained by the use of a Benedict closed circuit apparatus. The results were calculated according to the Harris-Benedict and the Aub-Du Bois standards, and the means of the two values were taken.

Tables 1 and 2 contain the results of the observations. In the first table are given the readings of the basal metabolism, pulse, respiration

and blood pressure as determined in the waking state and under hypnosis. From this it can be seen that the outstanding observations are those with the subject under hypnosis. Under hypnosis, not one case resulted in an increase of basal metabolism. All showed decreases ranging from 0.6 to 8.3 per cent, with an average decrease of 3.88 per cent. It will also be noted that in the majority of cases the pulse and respiration readings tended to be lower with the subjects under hypnosis than in the waking state.



The relation of the normal basal metabolism to that under hypnosis. The broken curve indicates the waking state; the solid curve, the hypnotic state.

The observations on blood pressure gave no constant changes.

As seen in table 2, the blood count and chemical analysis presented no characteristic variations with the subjects under hypnosis.

The accompanying chart gives a clear picture of the relationship of the normal basal metabolism to that with the subject under hypnosis.

COMMENT

A person may be under hypnosis without attaining mental and physical passivity—stray thoughts may pass through the mind, fear may

produce some disturbance or the body may be in an awkward position causing discomfort. But under proper hypnotic suggestions both mental and physical activities can be brought to a decidedly low working level. A basal metabolic rate taken under such conditions is representative of the metabolism of the body at a low degree of function.

The question arises as to the significance of an average decrease of 3.88 per cent in the basal metabolism under hypnosis. It is realized that such a drop in itself is of no importance, but when it appears consistently in every case it becomes of definite significance.

SUMMARY

The basal metabolism, pulse, respiration, blood count and chemical analysis of the blood of eighteen normal subjects were studied both in the waking state and in the hypnotic state.

In every case it was found that the basal metabolism was decreased under hypnotic suggestions tending to produce mental and physical inactivity. The decreases varied from 0.6 to 8.3 per cent, with an average decrease of 3.88 per cent.

There was a tendency for the pulse and respiration to be lower under hypnosis.

The blood pressure, blood count and chemical analysis of the blood showed no constant change under hypnosis.

CONCLUSIONS

Hypnotic suggestions tending to produce mental and physical inactivity decrease normal basal metabolism.

THE EFFECT OF LESSENED RESPIRATORY RESERVE ON THE BLOOD AND ON THE CIRCULATION

AN EXPERIMENTAL STUDY *

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The experimental study of respiratory reserve reported here is a continuation of similar work done a year ago. At that time, the efficiency of the mechanical factors of respiration received most attention. This study deals more particularly with the effects produced on the respiratory reserve by lessened mechanical efficiency. It represents an attempt to discover the point at which reserve is lost, at which respiration as a function is inadequate, and at which circulatory aid is required so that the animal can maintain a comfortable existence.

From among the group of animals under observation, an especially intelligent dog was chosen and was taught to lie quietly while wearing the usual mask employed in taking basal metabolic readings. This training was necessary before the undertaking of any of the operations that were employed and that were designed to lessen mechanical efficiency and to decrease vital capacity. The dog was vigorous and healthy in all respects, and was found to be organically healthy on careful general examination. Ether anesthesia was used in all operations, and strict surgical technic was employed.

OBSERVATIONS

First Period.—Operations.—On March 22, 1927, an attempt was made to section and perform evulsion of all the intercostal nerves on the left side. The first nerve was difficult to reach because of its normal inaccessibility. There is some doubt whether evulsion of it was effected. Portions of the lower eleven nerves were removed.

On March 31, a similar operation was done on the right side. Portions of the lower eight intercostal nerves were removed. The nerves were cut as near as possible to their spinal origins so that a large fraction of the intercostal muscles might be rendered functionless.

On April 7, with the use of the usual technic employed in phrenic neurectomy, evulsion of the right phrenic nerve was effected through an incision in the neck. With the same method of examination that was used in a former study, it was apparent that the right leaf of the diaphragm was totally paralyzed.

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* Work done in the Division of Experimental Surgery and Pathology, the Mayo Foundation.

On April 12, exeresis of the phrenic nerve was done on the left side.

Comment.—The muscular equipment on which respiratory competence depends was now limited to the muscles attached to the ribs on the vertebral side of the operative sites and to the extrarespiratory muscles about the neck and shoulders that are used by normal dogs only following severe muscular exertion. The respiratory function of the diaphragm was excluded; its effect on intra-abdominal pressure changes was removed; only its function as a partition separating the body cavity into two large portions remained.

The behavior of the dog was similar in all respects to that of the members of the large group formerly observed. It lived comfortably, played about like its normal mates, and on casual examination could not be distinguished from them. It could not, however, respond to vigorous exercise with the same ease because its vital capacity was lessened. The effect of the operative procedures on the dog was precisely like that of the former group and can be described by quoting the observations made on them as a whole:

"When the nerves are sectioned on only one side, there is immediate or delayed temporary or persisting asymmetry in the chest with a definite and measurable loss in the outward movement of the costal arch and margin during inspiration. When one-half of the diaphragm is paralyzed, the costal arch and margin do not increase their outward movement during inspiration either in man or dog. When the intercostal muscles on one side are paralyzed, the costal arch and margin continue to move away from the middle line even though the diaphragm is normal. These observations hold true whether they are made during the examination of experimental animals or of man following surgical procedure, accidents or disease. Moreover, the section of all the intercostal nerves on one side or on both sides, combined in whatever order possible with evulsion of one phrenic nerve or both phrenic nerves still leaves an animal capable of ordinary activities and with the ability to develop a vital capacity in excess of tidal air requirements. The introduction of phrenic neurectomy does not alter in any way the movement of the chest wall. Asymmetry and reduction of outward lateral movement occur when the intercostal nerves on one side are sectioned. The reduction amounts to from 30 to 50 per cent of normal depending on the number sectioned, and the movement of the chest wall is accomplished by muscles incapable of motion against the same resistance that would be overcome by normal muscles. Symmetry and bilateral reduction in movement result from bilateral section of the intercostal nerves. Regardless of the order in which the phrenic nerve paralysis is introduced, these movements remain the same.

"Vital capacity becomes progressively diminished and proportionately with the increase in muscular dysfunction produced by the several combined operations. When all the intercostal nerves are sectioned and both phrenic nerves cut, the animal cannot be anesthetized with ether without caution nor can he breathe comfortably through a spirometer while he is wearing the required mask. Vital capacity then is reduced almost to tidal air requirements."

These tests, however, had to deal with observations on functional behavior, and the consequences of operative intervention were expressed only in alterations of anteroposterior and transverse diameters during respiratory movements. Experiments designed to indicate alterations in volume were considered but were not technically simple enough to exclude a large percentage of error. It was decided to measure the intake of air for each unit of time following each operation and to compare the results with those obtained before starting any of the operative procedures, with the belief that the result would be the equivalent in value to alterations in volume. The data in table 1 represent the measurements after

each operation; those of the same dog before operation may serve as a control. The accompanying illustration is a tracing of respiratory movements, showing that the dog was lying quietly and breathing in a tranquil manner. Readings were not accepted unless this type of tracing accompanied them.

The dog was returned to the kennels and allowed to live under normal surroundings for a year. It was examined from time to time, but remarkable changes did not occur. Its general health improved; it became more playful than before the operations were done, and it gained in weight. Difficulty was not experienced either in urination or in defecation despite paralysis of the whole diaphragm and of the upper abdominal muscles. The muscles of the lower portion of the abdomen seemed to undergo hypertrophy; the abdominal wall was always rigid when examined. In other respects, the dog was bilaterally symmetrical; its respiratory movements were normal, and it was dyspneic only after unusual exertion. It could run up and down stairs without embarrassment.

TABLE 1.—*Effect of Operations on Vital Functions of a Dog* *

Dog 1	Weight, Kg.	Pulse Rate	Respiration Rate	Ventilation, Liters Each Minute
Normal	15.0	72	9	3.12
	....	95	14	3.65
	....	93	12	3.32
	....	65	14	2.64
Intercostal nerves cut on left side	14.6	86	13	3.18
	....	79	11	2.76
	....	77	11	2.72
	....	81	13	3.65
Intercostal nerves cut on right side	14.0	97	15	3.62
	....	89	15	3.75
	....	83	14	3.95
	....	101	16	3.91
Phrenic nerve cut on right side	13.8	73	11	2.62
	....	71	10	2.52
	....	66	10	2.48
	....	71	10	2.49
Phrenic nerve cut on left side	13.2	64	16	3.34
	....	78	16	2.94
	....	70	15	3.04
	....	75	16	3.35

* The figures indicate that the respiratory function was adequate to supply sufficient ventilation under all conditions and that the vital capacity provided for a normal amount of tidal air.

Second Period.—Operation.—On April 12, 1928, a year following the last previous operation, the abdominal cavity was opened and the diaphragm was resected from its ventral attachment. A single portion approximately 6 cm. in diameter and cut so that it involved both leaves was removed from the diaphragm. It was noted that the whole diaphragm had taken a position high in the thorax and that atrophy was so excessive that the usual color of the diaphragmatic muscle had faded to a light pink; the muscular portion could be distinguished from the tendinous portion only with difficulty, and the whole diaphragm had become so thinned that the lungs were plainly visible through it.

Comment.—The description of the operation just given is approximately in the words of the surgeon who operated. The condition described is exactly the same as that which I described in my earliest work on phrenic neurectomy. In the animal described in this paper, after paralysis of a year's duration, there was no suggestion of regeneration in any part of the diaphragm from the center to the periphery. The microscopic appearance was similar to that previously described and the vascularity of the musculature had the appearance of that of a normal diaphragm.

After a stormy convalescence in which dyspnea was the predominating symptom, the dog finally recovered and again lived a normal life. It learned to breathe differently, however. The chest was raised almost as one piece during inspiration and at the same time the lower part of the abdomen contracted strongly. This paradoxic abdominal movement suggested that perhaps the abdominal muscles were compensating for the loss of a competent diaphragmatic partition and were contracting during inspiration so that the abdominal contents might be retained within the abdomen and excluded from the thoracic cavity, thus preventing undue embarrassment or real respiratory incompetence.

It should be remembered that the dog is a pronograde animal of carnivorous habit, and the abdominal cavity has a relatively small visceral content. One could not predict the response of orthograde animals to similar treatment.

Moreover, the possibility of regeneration of intercostal nerves had to be kept constantly in mind. In other animals, however, in which evulsion of intercostal nerves had been performed, such regeneration had not been found at necropsy. From analogy, therefore, it was considered that an animal was now being studied in which, undisturbed, were five complete sets of intercostal muscles, vertebral muscles and the posterior portion of nineteen intercostal muscles as well as the accessory groups. Also, the lower portion of the abdominal muscles were acting

Kymograph record of respiration showing quiet breathing.

normally. The three functions of the diaphragm, respiratory, pressure-producing, and partition-effecting, were almost completely destroyed.

The dog was again allowed to live in the kennels and behaved as its normal mates.

Seven months later or twenty months from the date of the first operation, studies of the blood were made to determine whether or not the long continued reduction in vital capacity could have brought about erythrocytosis, change in blood volume, in the hematocrit volume, in the hemoglobin content, in the arterial and venous oxygen content or alterations in the blood count itself.

Readings of the intake of air for each unit of time were again made and were of the same character as those reported in table 1. The weight was 15.2 Kg. The surface temperature was 36.3 C. On the first test, the pulse rate was 66, the respiratory rate, 20, and the ventilation, in liters, each minute, was 3.96. On the second test, the corresponding figures were, respectively, 88, 18 and 4.56. From Nov. 14, 1928, to March 16, 1929, blood counts were recorded (table 2).

The hematocrit values were taken at various times from Nov. 16, 1928, to March 16, 1929. The values for erythrocytes were from 42 to 45 per cent, and for plasma from 55 to 58 per cent, which represent normal proportions.

Numerous tests of blood volume were made in the interval between November, 1928, and February, 1929, and a normal dog of equal weight and breeding was

used as a control. The volume estimations varied slightly but were always within normal limits. The last test on February 21 gave readings that were exactly the same for the control animal and for the test animal. Both dogs had 86 cc. of blood for each kilogram of body weight.

On Dec. 12, 1928, the readings for oxygen in per cent by volume were as follows: arterial oxygen content, 19.7 per cent, and venous oxygen content, 12.8 per cent. Oxygen capacity was 22.6; oxygen saturation was 87 per cent. The amount of hemoglobin was 16.9 Gm. in each hundred cubic centimeters of blood.

On Jan. 14, 1929, an electrocardiogram was taken, although abnormality of the heart had not appeared and its size had remained stationary. Roentgenographic examinations had been used to confirm general examinations. It was expected that the electrocardiographic reading would be normal, although the possibility of right ventricular preponderance was kept in mind. Yet any significant preponderance could hardly be expected in an animal the lungs and heart of which were equally unaffected organically. The electrocardiographic report was as follows: inversion of T wave in all three leads; sinus arrhythmia; sino-

TABLE 2.—*Blood Counts and Hematocrit Values on Various Dates After Operations*

				Differential Count, Per Cent *					
Date	Hemoglobin, Per Cent (Sahli)	Erythrocytes, Millions	Leukocytes, Thousands	Lymphocytes	Large Mononuclear Leukocytes	Transitionals	Neutrophils	Eosinophils	Cells by Hematocrit, Per Cent
11/14/28	120	7.43	5.7	14	2	2	78	4	....
11/16/28	....	....	....	..	..	..	..	..	45
12/ 3/28	115	5.86	9.3	18	4	2	72	4	....
12/27/28	120	6.07	9.7	15	1	6	78	..	42
1/15/29	130	6.71	5.0	8	..	15	69	8	45
2/18/29	....	....	....	..	..	..	..	..	43.3
2/21/29	95	6.25	5.6	..	..	22	74	2	....
2/27/29	95	6.38	9.2	..	..	..	..	..	....
3/ 8/29	85	4.91	15.7	..	..	..	..	..	....
3/16/29	90	5.76	12.4	..	..	..	..	..	42

* 200 cells were counted on each date.

auricular block; slight slurring of the Q R S wave in all three leads, and slight right ventricular preponderance. This is essentially normal for a dog and does not indicate that the respiratory reserve had been reduced to such a degree of decompensation as to require unusual cardiac cooperation.

All tests of circulation and of the blood itself confirm the belief that this dog still retained sufficient respiratory reserve so that it did not require assistance from the circulation to maintain its competence under ordinary living conditions. The readings were taken after a long interval of time to avoid alterations, such as compensatory erythrocytosis, that might have been anticipated at an earlier date and in which I was not especially interested.

Third Period.—Operation.—On Feb. 28, 1929, the dog's abdominal cavity was again opened. Roentgenographic examinations had shown that the stomach had migrated into the pleural space. When adhesions had been broken down, it was discovered that the whole stomach, a part of the duodenum, and all but two of the lobes of the liver had forced their way into the thorax. That part of the diaphragm remaining presented the appearance elsewhere described. It was thin, translucent and flapped back and forth with respiratory movements. It was caught with forceps, drawn downward and an incision was made parallel to the costal attachment, the diaphragm being detached from side to side and backward

as far as possible. The strip of diaphragm between the line of incision and the aperture originally made was not removed.

Comment.—After recovery from the anesthetic, the dog ran about the recovery room seemingly unembarrassed in its breathing. The dog's recovery has been quite uneventful, but the animal has been kept at rest. The regimen of rest has been imposed so that healing might not be interfered with, but more so that compensation might be developed and unnecessary strain might not be put on the function of respiration. Examination of the blood on March 8 and 16 gave the following results, respectively: hemoglobin, 85 and 90 per cent; erythrocytes, 4,910,000 and 5,760,000, and leukocytes, 15,900 and 12,400 in each cubic millimeter. The differential count of the leukocytes showed them to be present in normal proportions. The per cent by volume of the erythrocytes was relatively normal, according to the hematocrit reading.

The volume of air breathed each minute was again measured and was found to be somewhat larger than that previously recorded. Three estimations each were made of pulse rate, respiratory rate and ventilation in liters each minute. The results were as follows: pulse rate, 76, 82 and 80; respiratory rate, 22, 22, and 22, and ventilation in liters each minute, 4.64, 4.75 and 4.31. Surface temperature and air temperature also were taken three times, in degrees centigrade, with the following results: surface temperature, 36.4, 37.6 and 37.2; air temperature, 21.4, 27.0 and 24.0.

On March 20, 1929, the dog was healthy and active, and did not show evidence of respiratory embarrassment. The lowered percentage of hemoglobin, a reduced erythrocyte count and an attendant rise in the number of leukocytes were the only alterations that had appeared since the last operation. The ventilation each minute has increased but has reached only high normal values.

SUMMARY AND CONCLUSIONS

In this study of the respiratory reserve, the muscles ordinarily responsible for the production of inspiration and expiration have been rendered functionless in whole or in part by evulsion of their motor nerve trunks. All of the several functions of the diaphragm have been interfered with so that a state characteristic of a mammal has been changed, and the final state is one that, in respect to the diaphragm, virtually is characteristic more of birds than of mammals.

Vital capacity has been lessened but never beyond the point where it failed to be equivalent to tidal air. The ventilation in liters of air breathed each minute reached a high normal amount but was not distinctly abnormal at any time.

The hemoglobin decreased from high to low normal percentages, but the amount of hemoglobin for each hundred cc. of blood was within normal limits.

The hematocrit percentages varied slightly but were never abnormal.

The arterial and the venous oxygen content and the oxygen of the blood were essentially normal. However, oxygen saturation of both arterial and venous blood was lowered. The number of erythrocytes failed to indicate either temporary or permanent erythrocytosis such as might have been anticipated had respiratory competence been destroyed.

The heart has remained normal functionally, has not shown evidence of hypertrophy, and the electrocardiogram cannot be interpreted as evidence to indicate any definite failure of the right ventricle.

The experiment illustrates the degree to which muscular dysfunction may be carried before respiratory incompetence develops in an animal which has a normal heart and normal lungs. It seems to confirm the independence of two fundamental functions having interrelated duties; great loss of reserve in one is required before demonstrable evidence of cooperative support is provided by the other.

EXOPHTHALMIC GOITER

THE PROTEIN CONTENT OF THE CEREBROSPINAL FLUID*

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One of us (W.O.T.) has previously shown that the concentration of protein in cerebrospinal fluid is high in most cases of myxedema, and usually drops to within normal limits following the administration of desiccated thyroid.[1] Similar measurements[2] have now been made in several cases of exophthalmic goiter before any treatment was started and after the body weight had reached a stationary level following a subtotal thyroidectomy. The observations are the opposite of those in myxedema. Before treatment, the concentration of protein is usually within the lower limits of normal.[3] It shows a well marked increase (eleven out of fifteen cases) in association with a gain in body weight and a reduction in basal metabolism after operation. This is illustrated in fifteen unselected cases in the accompanying table and illustration. It may be noted that, as usual, there are wide individual variations in protein concentration. Our experience has been, however, that at least in patients with myxedema, the concentration is relatively constant in each case during a stationary state.

In one patient whose thyroid gland was apparently functioning normally, we were able to observe the effect of the administration of thyroid on the concentration of protein in spinal fluid. A well marked increase in basal metabolism during its administration was associated with a well marked decrease in the concentration of protein.

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* From the Metabolism and Neurological Laboratories of the Massachusetts General Hospital.

1. Thompson, W. O.; Thompson, P. K.; Silveus, E., and Dailey, M. E.: The Protein Content of the Cerebrospinal Fluid in Myxedema, J. Clin. Investigation **6**:251, 1928.

2. The method of Denis and Ayer (Method for Quantitative Determination of Protein in Cerebrospinal Fluid, Arch. Int. Med. **26**:436 [Oct.] 1920) was used. The error of this method is not greater than 5 per cent. The spinal fluid was always removed under "basal" conditions.

3. The normal values are considered to be about 20 to 45 mg. per hundred cubic centimeters.

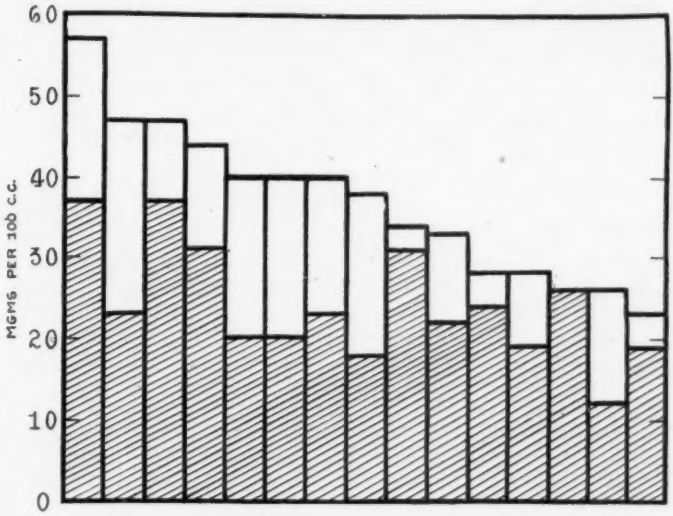
The Concentration of Protein in Cerebrospinal Fluid in Fifteen Unselected Cases of Exophthalmic Goiter Before and After a Subtotal Thyroidectomy *

Patient			Before a Subtotal Thyroidectomy				After a Subtotal Thyroidectomy				
Age	Initials	Sex	Days Before Operation	Basal Metabolic Rate, Per Cent Normal	Weight, Kg.	Concentration of Protein in Spinal Fluid, Mg. per 100 Cc.	Days After Operation	Basal Metabolic Rate, Per Cent Normal	Weight, Kg.	Concentration of Protein in Spinal Fluid, Mg. per 100 Cc.	Change in Protein Concentration, Mg. per 100 Cc.
42	P. M.	M	23	+63	62.2	37	78	+ 9	70.5	57	+20
38	J. B.	M	22	+52	51.3	22	70	— 6	61.8	47	+24
36	M. M.	F	13	+29	54.0	37	90	— 6	61.7	47	+10
38	M. C.	F	6	+18	66.3	31	103	—12	72.0	44	+13
17	B. D.	F †	7	+20	68.2	20	90	—21	71.7	40	+20
40	J. C.	M	69	+71	59.6	20	49	+33	72.3	40	+20
16	E. M.	F	19	+39	41.7	23	57	+ 2	52.5	40	+17
55	W. M.	M	24	+33	52.8	18	70	— 5	67.9	38	+20
18	E. F.	F	23	+57	43.6	31	37	— 7	45.5	34	+ 3
41	I. E. C.	M	24	+72	68.9	22	66	+29	68.5	33	+11
43	E. K.	M	18	+45	61.6	24	78	— 8	71.9	28	+ 4
18	V. G.	F ‡	7	+60	52.3	19	161	+29	55.4	28	+ 9
27	L. B.	M	22	+62	57.5	26	122	+ 8	70.5	26	0
42	A. G.	F †	10	+48	47.5	13	490	—19	58.7	26	+14
17	M. P.	F ‡	22	+35	43.1	19	104	+15	46.5	23	+ 4
	Average...		..	+47	55.4	24	...	+ 3	63.2	37	+13

* In every instance, the concentration of protein recorded is that of the first 2 or 3 cc. removed from the lumbar region.

† In these two patients, the low basal metabolism after operation was not associated with an underfunction of the thyroid so far as could be clinically determined.

‡ In these instances two hemithyroidectomies were done, and the time after operation is the time after the second hemithyroidectomy. In V. G., the time before operation is the time before the second hemithyroidectomy; in M. P., it is the time before the first hemithyroidectomy.



The concentration of protein in spinal fluid in fifteen unselected cases of exophthalmic goiter, before (cross-hatched areas) and after (total height of columns) a subtotal thyroidectomy. The data are plotted in the order recorded in the table. In the thirteenth case, no change was noted.

The cause of these changes in protein concentration in myxedema and in exophthalmic goiter is uncertain. It has been previously suggested [4] that they may be related in some manner to the increase in the storage of nitrogenous substances in myxedema and the apparent decrease in exophthalmic goiter.[5] In any case, it seems to be satisfactorily established that the thyroid gland is an important factor in controlling the protein content of the cerebrospinal fluid.

It was observed that headaches following the lumbar punctures were more frequent before than after operation. Moreover, they were more frequent in patients with exophthalmic goiter preceding operation than in the patients with myxedema previously reported.[1]

CONCLUSION

The concentration of protein in the cerebrospinal fluid is within the lower limits of normal in most cases of exophthalmic goiter and usually shows a well marked increase, in association with a gain in weight and reduction in basal metabolism following a subtotal thyroidectomy.

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4. Footnote 1. Thompson, W. O.; Thompson, P. K.; Silveus, E., and Dailey, M. E.: The Cerebrospinal Fluid in Myxedema, Arch. Int. Med., to be published.

5. Magnus-Levy, A.: Metabolism in Diseases of the Ductless Glands, in Van Noorden, C.: Metabolism and Practical Medicine, Chicago, W. T. Keener and Company, 1907, vol. 3, p. 983. Boothby, W. M.; Sandiford, I.; Sandiford, K., and Slosse, J.: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects, Tr. A. Am. Phys. **40**:195, 1925.

THE BASAL METABOLIC RATE IN RELATION TO THE MENSTRUAL CYCLE*

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As the previous work on the basal metabolic rate in relation to the menstrual cycle has been reviewed in practically every paper on the subject, we need mention only that of Griffith and his collaborators (1929).[1] Their results indicate a positive correlation. Although their data have not been treated statistically, the paper seems to be the best published to date. In the work described here, the Benedict-Roth apparatus was used. All the necessary precautions were observed in making the determinations. The determinations were made almost daily on ten different subjects throughout one or more menstrual cycles. The subjects were normal women without the complicating factor—menstrual pain (Boothby and Sandiford, 1924).[2] The surface areas were determined by the height-weight formula of DuBois.

In order to ascertain whether there is a relationship between the basal metabolic rate and the menstrual cycle, the cycle was divided into four periods: menstrual, postmenstrual, intermenstrual and premenstrual. The periods were considered of equal duration except in the case of the menstrual period, which is self-determined.

Table 1 gives the basal metabolic rate as determined. In table 2 the frequency distributions are shown with the average values for each period. Table 3 gives the standard deviation from the average for each series and the probable error of the average of each period of the cycle. The probable error of the average of each period is based on the standard deviation from the average for the series. The exception to this is the series for the entire group. In this case the probable error

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* From the Laboratory of Physiological Chemistry, University of Minnesota.

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1. Griffith, F. R. Jr.; Pucher, G. W.; Brownell, K. A.; Klein, J. D., and Carmer, M. E.: Studies in Human Physiology: I. The Metabolism and Body Temperature under Basal Conditions, Am. J. Physiol. **87**:602, 1929.

2. Boothby, W. M., and Sandiford, I.: Basal Metabolism, Physiol. Rev. **55**:69, 1924.

TABLE 1.—*Basal Metabolic Rates*

Subject, M. G.; 20 Years; 1.58 Sq.M.

	Date	Calories per Sq.M. per Hr.
Intermenstrual	Feb. 12	34.0
	13	34.4
	14	36.7
	15	35.2
Premenstrual	16	33.8
	17	35.0
	18	33.5
	19	36.1
	20	36.7
	21	33.5
	22	33.4
	23	32.1
	24	33.6
Menstrual	25	32.7
	26	38.5
Menstrual	Feb. 27	34.2
	28	33.4
	Mar. 1	32.2
Postmen-	2	32.2
strual	3	33.2
	4	32.8
	5	33.0
	6	32.6
	7	33.1
	8	34.0
	9	32.4
	10	32.8
Intermenstrual	11	32.1
	12	33.0

Subject, L. G.; 23 Years; 1.55 Sq.M.

	Date	Calories per Sq.M. per Hr.
Postmenstrual	Feb. 16	31.5
Intermen-	17	31.9
strual	18	33.3
	19	32.7
	20	32.8
	21	31.6
	22	31.4
Premenstrual	23	32.5
	24	32.5
	25	33.7
	26	34.9
	27	33.9
	28	33.3
Menstrual	Mar. 1	31.8
	2	31.8
Menstrual	Mar. 3	31.6
	4	30.9
	5	31.6
Postmenstrual	6	33.0
	7	33.6
	8	30.0
	9	32.1
	10	32.3
	11	33.3
Intermenstrual	12	31.1
	13	32.7
	14	32.3
	15	35.1
	16	31.8

Subject, M. S.; 35 Years; 1.67 Sq.M.

	Date	Calories per Sq.M. per Hr.
Postmenstrual	Oct. 30	34.3
	Nov. 1	35.5
	3	35.0
	5	35.5
Intermenstrual	7	34.9
	8	38.8
	9	33.1
	10	33.9
	11	35.4
	13	36.6
Premenstrual	14	37.3
	15	34.5
	16	35.0
Premenstrual	Nov. 17	36.7
	18	38.5
	19	35.1
	20	36.5
	21	36.9
Menstrual	22	36.4
	23	34.6
	24	35.4
	25	30.9
Postmenstrual	26	33.8
	28	34.0
	29	33.0

Subject, Eva S.; 22 Years; 1.64 Sq.M.

	Date	Calories per Sq.M. per Hr.
Premenstrual	Feb. 15	36.9
	16	38.5
	18	41.3
	19	42.7
	20	34.8
	21	36.0
Menstrual	22	36.3
	23	35.9
	25	31.5
Postmenstrual	26	29.1
	27	33.0
	28	33.9
	Mar. 1	36.0
Postmenstrual	Mar. 2	36.9
	4	34.4
	5	34.0
	6	33.6
Intermenstrual	7	36.7
	8	31.4
	9	37.5
	12	34.6
	13	36.1
	14	37.0
	15	35.8
Premenstrual	16	36.4

Subject, E. T.; 20 Years; 1.73 Sq.M.

	Date	Calories per Sq.M. per Hr.
Intermenstrual	Oct. 30	30.7
	31	31.9
Premen-	Nov. 1	31.3
strual	2	32.3
	3	31.3
	4	31.5
	5	33.2
Menstrual	6	30.9
	7	31.0
	8	30.0
	9	30.1
	10	31.2
	11	32.0
Postmenstrual	13	31.5
	15	31.0
	16	28.7
Intermenstrual	17	30.1
	18	29.9
	19	30.7
	20	30.3
Intermenstrual	Nov. 21	35.0
	22	32.5
Premenstrual	23	31.6
	25	31.3
	26	31.0
	27	28.7
Menstrual	28	30.6
	29	30.2
	30	27.8
	Dec. 2	30.5
	3	29.7
Postmenstrual	4	28.6
	5	28.1
	6	30.9
	7	31.0
	8	29.5
Intermenstrual	9	30.7
	10	29.4
	11	29.2

Subject, G. W.; 20 Years; 1.52 Sq.M.

	Date	Calories per Sq.M. per Hr.
Menstrual	Jan. 29	31.3
	30	31.0
	31	34.0
	Feb. 1	34.3
	2	34.1
	3	33.2
	4	31.8
Postmenstrual	5	32.0
	6	33.1
	7	33.7
	8	32.1
	9	33.1
	10	30.5
Intermenstrual	11	33.3
	12	30.9
	13	32.3
	14	32.4
	15	32.9
	16	32.3
Premenstrual	17	32.8
Premenstrual	Feb. 18	33.2
	19	33.9
	20	34.1
	21	32.7
	22	35.3
Menstrual	23	31.8
	24	30.6
	25	32.4
	26	31.8
	27	31.8
	28	30.5
	Mar. 1	31.8
	2	30.5
Postmenstrual	3	30.9
	4	32.1
	5	33.7
	6	32.9
	7	30.9
	8	33.3

Subject, C. C.; 22 Years; 1.63 Sq.M.

	Date	Calories per Sq.M. per Hr.
Postmenstrual	Aug. 1	34.1
	2	33.8
	3	33.9
Intermenstrual	4	33.6
	5	33.2
	6	33.5
	7	32.6
	8	35.0
	9	35.1
	10	36.8
Premenstrual	11	33.5
	13	35.6
	14	34.5
	15	35.7
	16	33.9
	17	33.7
	18	33.4
Menstrual	20	35.8
	21	31.7
	22	33.8
	23	32.7
Postmenstrual	Aug. 24	32.8
	25	31.5
	27	34.1
	28	34.5
Premen-	Oct. 10	34.3
strual	11	34.8
Menstrual	12	32.4
	13	32.3
	14	32.8
	15	34.4
	16	32.5
Postmenstrual	17	31.2
	18	31.3
	19	31.9
	20	30.3
	21	32.0
	22	30.6
Intermenstrual	23	30.1
	24	31.6
	25	31.6
	26	31.8
Intermenstrual	Oct. 27	32.2
	28	31.3
	29	32.1
	30	31.9
	31	30.1
Premen-	Nov. 1	31.5
strual	2	31.3
	3	33.4
Menstrual	8	31.9
	9	31.5
	10	30.3
Postmenstrual	11	32.6
	12	33.4
	13	31.5
	14	30.8
	15	29.5
	16	29.1
Intermenstrual	17	30.6
	18	32.1
	19	29.9
	20	30.0
Intermenstrual	Nov. 21	28.8
	22	29.7
Premenstrual	23	29.2
	24	30.2
	25	31.2
	26	30.1
	27	28.0
	28	29.7
Menstrual	29	29.1
	30	28.6
Postmen-	Dec. 1	29.2
strual	2	29.7
	3	29.8
	4	28.1
	5	27.8
	6	29.4
	7	29.8
Intermenstrual	8	29.7
	9	29.3
	10	30.3
	11	33.3

TABLE 1.—*Basal Metabolic Rates—Continued*

Subject, P. O.; 22 Years; 1.61 Sq.M.

Date	Calories per Sq.M. per Hr.	Date	Calories per Sq.M. per Hr.	Date	Calories per Sq.M. per Hr.	Date	Calories per Sq.M. per Hr.
Intermenstrual		Postmenstrual		Postmenstrual		Premenstrual	
July 31	32.8	Aug. 24	28.9	Oct. 27	29.4	Nov. 23	26.0
Aug. 2	31.6	25	29.0	28	31.0	Menstrual 24	32.4
3	31.7	Intermenstrual 27	29.6	29	29.8	25	29.7
4	30.7	28	27.8	30	30.9	26	27.7
Premenstrual 5	30.7	Oct. 10	31.2	31	31.3	27	29.0
6	30.4	11	31.0	Nov. 1	29.3	28	30.2
7	32.4	Premenstrual 12	30.3	2	30.2	Postmenstrual 30	28.8
8	31.9	13	30.9	3	28.6	Dec. 1	29.2
9	31.3	14	31.2	Intermenstrual 8	30.7	2	28.0
10	31.5	15	29.3	9	33.1	3	28.6
11	31.3	16	30.2	10	30.6	4	30.6
13	30.4	17	30.7	13	31.3	5	30.8
Menstrual 14	32.5	18	30.5	14	31.8	6	33.2
15	31.1	19	31.2	Premenstrual 15	30.3	7	30.8
16	30.0	20	31.8	16	30.4	8	30.1
17	28.9	Menstrual 21	30.1	17	30.6	Intermenstrual 9	28.9
Postmenstrual 18	30.5	22	30.8	18	31.7	10	29.9
20	30.9	23	30.6	19	29.2	11	29.3
21	30.2	24	32.2	20	29.4	12	29.4
22	31.0	25	30.0	21	29.4	13	30.6
23	29.3	Postmenstrual 26	32.3	22	30.6	14	28.8

Subject, E. S.; 21 Years; 1.48 Sq.M.

Date	Calories per Sq.M. per Hr.	Date	Calories per Sq.M. per Hr.	Date	Calories per Sq.M. per Hr.	Date	Calories per Sq.M. per Hr.
Intermenstrual		Menstrual		Intermenstrual		Premenstrual	
Oct. 10	36.8	Oct. 24	37.0	Nov. 7	33.8	Nov. 21	37.1
11	35.5	25	37.2	8	38.1	22	38.1
12	37.1	26	35.6	9	37.5	23	39.0
14	38.1	27	36.6	10	38.3	24	38.8
15	36.3	28	37.0	11	37.3	Menstrual 25	36.4
Premenstrual 16	38.2	29	37.1	12	38.8	27	33.0
17	35.5	Postmenstrual 30	36.8	13	38.4	28	37.8
19	36.3	31	38.4	14	38.3	29	37.4
20	41.5	Nov. 1	36.3	15	36.6	Postmen- Dec. 1	33.7
21	38.9	2	36.6	Premenstrual 16	37.6	strual 2	39.1
22	38.1	3	36.5	18	36.4	3	36.3
23	37.5	4	33.3	19	38.9	4	38.2
		5	38.1	20	36.2	5	40.7

Subject, H. R.; 23 Years; 1.59 Sq.M.

Date	Calories per Sq.M. per Hr.	Date	Calories per Sq.M. per Hr.	Date	Calories per Sq.M. per Hr.	Date	Calories per Sq.M. per Hr.
Menstrual		Intermenstrual		Premenstrual		Menstrual	
Feb. 5	33.5	Feb. 15	31.7	Feb. 23	30.9	Mar. 4	31.6
6	33.2	16	31.0	25	32.8	5	31.3
7	33.7	17	35.4	26	31.9	6	30.3
8	35.6	18	31.5	27	30.3	Postmenstrual 7	31.3
Postmenstrual 9	32.3	19	33.5	28	31.7	8	32.8
10	32.4	20	33.2	Menstrual Mar. 1	32.8	9	32.6
11	31.7	21	31.4	2	32.7	11	31.5
12	32.2	22	30.2	3	33.3	12	32.9
13	31.6						

of the average of each period is based on the standard deviation from the average of that period. It is only in this one case that the number of determinations warrants this treatment.

Chart 1 is simply a graphic representation of the daily determinations for each subject. Chart 2 shows the averages of table 2 plotted with respect to the probable errors of table 3. The rectangles represent the probable errors.

As noted in chart 2, the results indicate a definite trend toward a lowered rate either during or following menstruation and a premenstrual rise. This is especially significant in averages for the entire group. We cannot explain the one contradictory case, that of H. R.

In general, the curves obtained correspond to those of Wildebush and McClendon (1929) [3] for concentration of ovarian hormone in the circulating blood.

Included in the foregoing data is one special case—that of C. C. This subject was made a special case in order to eliminate the factors, diet and muscular activity, which affect the basal metabolic rate (Benedict, 1915 [4]) (Helmreich, 1924 [5]) (Wishart, 1927, 1928 [6]).

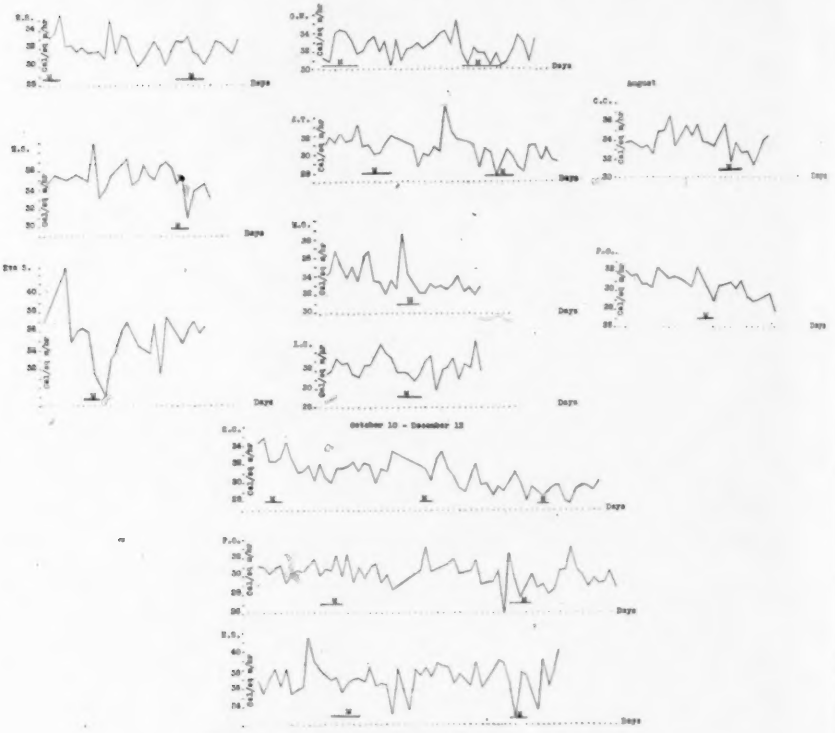

Chart 1.—Metabolic charts of the women studied.

3. Wildebush, F. F., and McClendon, J. F.: A Method for Assay of Ovarian Hormone in Blood and Urine and the Relation of the Assay to the Menstrual Cycle, Proc. Soc. Exper. Biol. & Med. **27**:785, 1929.

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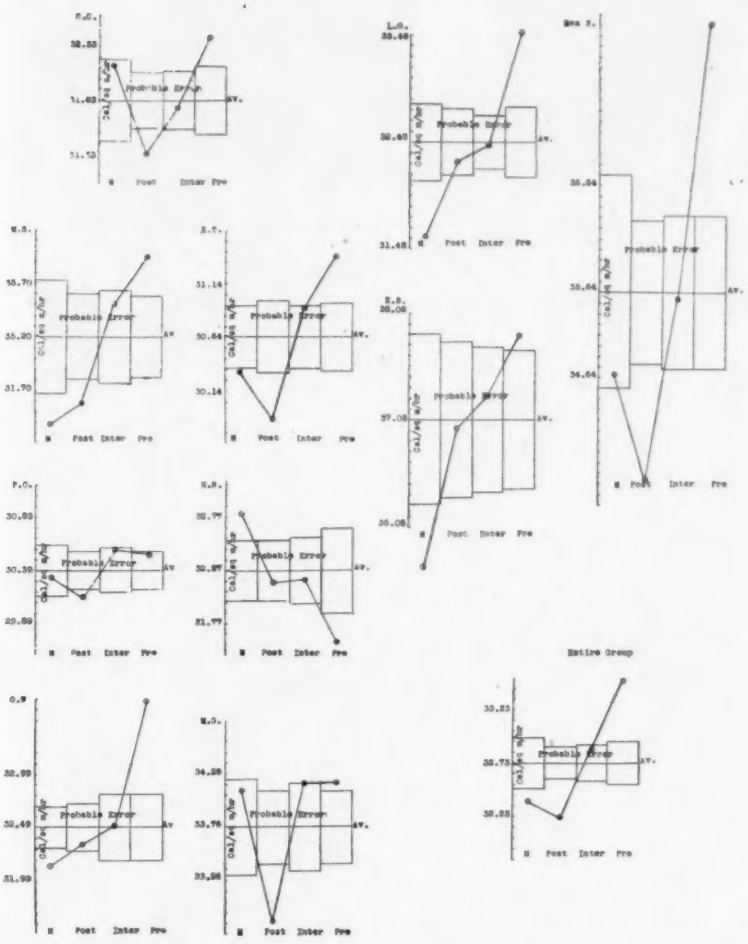

Chart 2.—Graph showing the variation in basal metabolic rate of women during the menstrual cycle. The calories per square meter per hour are noted on the ordinate and the periods—menstrual, postmenstrual, intermenstrual and premenstrual—on the abscissa. The circles denote the averages for the periods. The horizontal line denotes the grand average, and the rectangles denote the probable errors for the periods. Where the circle lies inside the rectangle, the results are within the probable errors and therefore do not show a significant variation from the grand average.

TABLE 2.—*Frequency Distributions, with Average Values for Each Period*

Subject H. R.	Calories per Sq. M. per Hour													No. of Determinations	Average Calories per Sq. M. per Hour
Periods	28	28.5	29.5	30	30.5	31	31.5	32	32.5	33	33.5	34	35	35.5	
Menstrual	..	..	..	..	1	..	2	..	1	2	3	..	..	1	10	32.80
Postmenstrual	..	..	..	..	..	..	4	1	3	2	..	..	..	..	10	32.15
Intermenstrual	..	..	..	1	..	1	3	..	..	1	1	..	..	1	8	32.19
Premenstrual	..	..	..	..	1	1	1	1	..	1	..	..	..	..	5	31.60
Total	..	..	..	1	2	2	10	2	4	6	4	..	..	2	23	32.27

Subject M. G.	Calories per Sq. M. per Hour													No. of Determinations	Average Calories per Sq. M. per Hour
Periods	32	32.5	33	33.5	34	34.5	35	35.5	36	36.5	37	37.5	38	38.5	
Menstrual	1	1	..	1	1	..	..	..	..	..	..	..	..	1	5	34.1
Postmenstrual	1	2	5	..	1	..	..	..	..	..	..	..	..	..	9	32.89
Intermenstrual	1	..	1	..	1	1	1	..	..	1	..	..	..	..	6	34.17
Premenstrual	1	..	..	4	1	..	1	..	1	1	..	..	..	..	9	34.17
Total	4	3	6	5	4	1	2	..	1	2	..	..	..	1	29	33.76

Subject G. W.	Calories per Sq. M. per Hour										No. of Determinations	Average Calories per Sq. M. per Hour
Periods	30.5	31	31.5	32	32.5	33	33.5	34	34.5	25	35.5	
Menstrual	3	1	1	5	1	1	..	2	1	..	..	15	32.13
Postmenstrual	1	2	..	3	..	3	3	..	..	..	..	12	32.33
Intermenstrual	..	1	..	..	3	1	1	..	..	..	..	6	32.5
Premenstrual	..	..	..	..	1	2	..	2	..	..	1	6	33.67
Total	4	4	1	8	5	7	4	4	1	..	1	29	32.49

Subject L. G.	Calories per Sq. M. per Hour										No. of Determinations	Average Calories per Sq. M. per Hour
Periods	30	30.5	31	31.5	32	32.5	33	33.5	34	34.5	35	
Menstrual	..	..	1	2	2	..	..	..	..	..	..	5	31.60
Postmenstrual	1	..	..	1	1	1	1	2	..	..	..	7	32.29
Intermenstrual	..	..	1	2	2	3	1	1	..	..	1	11	32.45
Premenstrual	..	..	..	..	..	2	..	2	1	..	1	6	33.50
Total	1	..	2	5	5	6	2	5	1	..	2	29	32.48

Subject M. S.

Periods	Calories per Sq. M. per Hour															
	31	33	33.5	34	34.5	35	35.5	36	36.5	37	37.5	38	38.5	39		
Menstrual	1	..	..	..	1	..	1	..	1	..	..	..	..	..	4	34.38
Postmenstrual	..	1	..	1	2	1	2	..	..	..	..	..	..	..	7	34.57
Intermenstrual	..	1	..	1	..	1	1	..	1	..	..	..	..	1	6	35.5
Premenstrual	..	..	..	..	1	2	1	..	2	1	1	..	..	..	8	35.94
Total	1	2	..	2	4	4	5	..	4	1	1	..	..	1	25	35.20

Subject E. T.

Periods	Calories per Sq. M. per Hour															
	28	28.5	29	29.5	30	30.5	31	31.5	32	32.5	33	33.5	34	35		
Menstrual	1	..	..	1	3	2	3	..	1	..	..	..	..	..	11	30.32
Postmenstrual	1	2	..	1	..	..	3	1	..	..	..	..	..	..	8	29.88
Intermenstrual	..	..	1	1	2	4	..	..	1	1	..	..	..	1	11	30.91
Premenstrual	..	1	..	..	..	..	1	5	..	1	1	..	..	..	9	31.39
Total	2	3	1	3	5	6	7	6	2	2	1	..	..	1	39	30.64

Subject Eva S.

Periods	Calories per Sq. M. per Hour																			
	29	31.5	32	33	33.5	34	34.5	35	35.5	36	36.5	37	37.5	38	38.5	39	40	41.5	42.5	
Menstrual	..	1	..	..	..	..	..	..	..	1	1	..	..	..	..	..	..	..	..	3	34.67
Postmenstrual	1	..	..	1	1	2	1	..	..	1	..	1	..	..	..	..	..	..	..	8	33.88
Intermenstrual	..	1	..	..	..	.	1	..	..	2	1	1	1	..	..	..	..	..	..	7	35.57
Premenstrual	..	..	..	..	..	..	..	1	..	1	1	1	..	..	1	..	..	1	1	7	38.14
Total	1	2	..	1	1	2	2	1	..	5	3	3	1	..	1	..	..	1	1	25	35.64

Subject C. C.

Periods	Calories per Sq. M. per Hour																			
	28	28.5	29	29.5	30	30.5	31	31.5	32	32.5	33	33.5	34	34.5	35	35.5	36	36.5	37	
Menstrual	..	1	1	..	..	1	..	2	1	3	1	..	1	1	..	..	1	..	..	13	32.15
Postmenstrual	2	..	2	3	2	2	2	3	2	2	1	1	4	1	..	..	..	..	..	27	31.33
Intermenstrual	..	..	1	3	4	2	..	3	5	1	1	3	..	..	2	..	..	..	1	26	31.77
Premenstrual	1	..	1	1	2	..	1	2	..	..	..	4	1	2	1	2	..	..	..	18	32.42
Total	3	1	5	7	8	5	3	10	8	6	3	8	6	4	3	2	1	..	1	84	31.83

TABLE 2.—*Frequency Distributions, with Average Values for Each Period—Continued*

Subject P. O.	Calories per Sq. M. per Hour														No. of Determinations	Average Calories per Sq. M. per Hour
Periods	26	26.5	27	27.5	28	28.5	29	29.5	30	30.5	31	31.5	32	32.5	33	
Menstrual	..	..	..	1	..	..	2	1	4	1	2	..	1	2	..	14	30.32
Postmenstrual	..	..	..	..	1	2	4	3	4	2	6	1	..	1	1	25	30.14
Intermenstrual	..	..	..	..	1	..	2	3	1	4	2	3	1	..	2	19	30.58
Premenstrual	1	..	..	..	..	..	1	3	1	10	3	4	2	1	..	26	30.54
Total	1	..	..	1	2	2	9	10	10	17	13	8	4	4	3	84	30.39

Subject E. S.	Calories per Sq. M. per Hour															
Periods	33	33.5	34	34.5	35	35.5	36	36.5	37	37.5	38	38.5	39	40.5	41.5	
Menstrual	1	..	..	..	..	1	..	2	4	1	1	..	..	..	..	10	35.70
Postmenstrual	..	2	..	..	..	..	..	4	1	..	2	1	1	1	..	12	37.00
Intermenstrual	..	..	1	..	..	1	..	2	2	2	2	3	1	..	..	14	37.29
Premenstrual	..	..	..	..	..	1	1	2	1	2	3	..	4	..	1	15	37.87
Total	1	2	1	..	..	3	1	10	8	5	8	4	6	1	1	51	37.08

Entire Group		
Period	N (No. of Determinations)	X Calories per Sq. M. per Hour
Menstrual	90	32.37
Postmenstrual	125	32.22
Intermenstrual	114	32.86
Premenstrual	109	33.50
Total	438	32.73

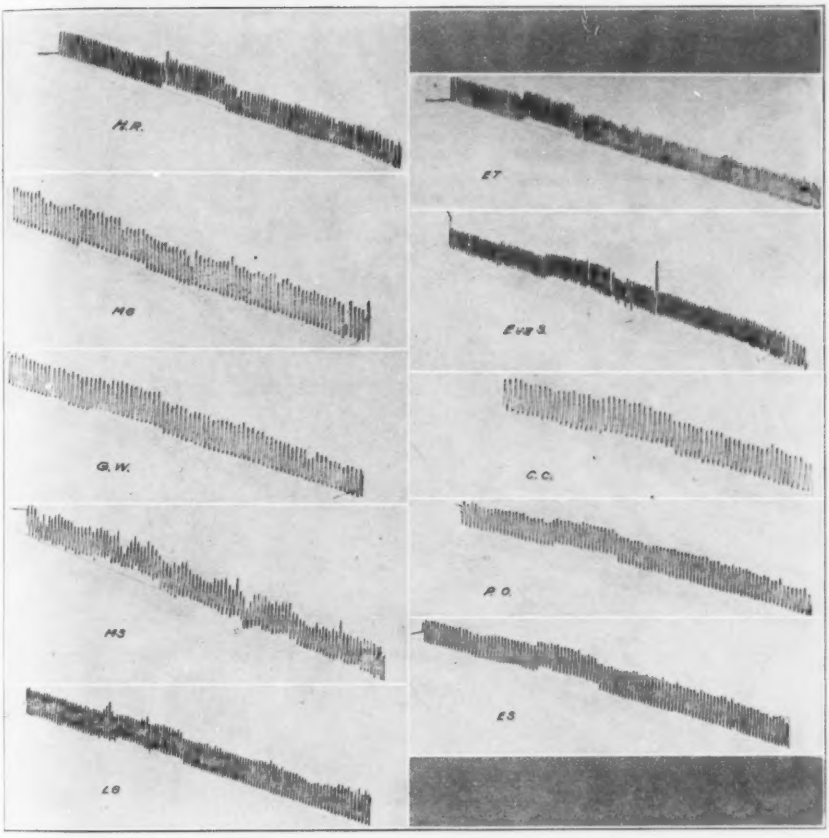

Chart 3.—Tracing on the Benedict-Collins apparatus during the characteristic respiratory habits of the ten women.

TABLE 3.—*Standard Deviations from the Average for Each Series and Probable Error of the Average of Each Period of the Cycle*

	Menstrual		Postmenstrual		Intermenstrual		Premenstrual		Series:	
Subject	Average Calories per Sq.M. per Hour	Probable Error	Average Calories per Sq.M. per Hour	Probable Error	Average Calories per Sq.M. per Hour	Probable Error	Average Calories per Sq.M. per Hour	Probable Error	Average Calories per Sq.M. per Hour	Standard Deviation from Series (Aver.)
E. S.	35.70	±0.8016	37.00	±0.7317	37.29	±0.6774	37.87	±0.6545	37.08	3.7580
P. O.	30.32	±0.2418	30.14	±0.1809	30.58	±0.2076	30.54	±0.1774	30.39	1.3413
C. C.	32.15	±0.3793	31.33	±0.2632	31.77	±0.2682	32.42	±0.3223	31.83	2.0273
H. R.	32.80	±0.2780	32.15	±0.280	32.19	±0.3130	31.60	±0.3060	32.27	1.3126
Eva S.	34.67	±1.1008	33.88	±0.6741	35.57	±0.7206	38.14	±0.7206	35.64	2.8267
M. G.	34.10	±0.4502	32.89	±0.3356	34.17	±0.4110	34.17	±0.3356	33.76	1.4926
G. W.	32.13	±0.1944	32.33	±0.2174	32.50	±0.3074	33.67	±0.3074	32.49	1.1166
M. S.	34.38	±0.5332	34.57	±0.4031	35.50	±0.4354	35.94	±0.3771	35.20	1.581
E. T.	30.32	±0.2902	29.88	±0.3403	30.91	±0.2902	31.39	±0.3209	30.64	1.4271
L. G.	31.60	±0.3649	32.29	±0.3084	32.45	±0.2460	33.50	±0.3331	32.48	1.2097

	Entire Group		
Period	Average Calories per Sq.M. per Hour	Probable Error	Standard Deviation from Average
Menstrual	32.37	±0.2409	3.3887
Postmenstrual	32.22	±0.1475	2.4445
Intermenstrual	32.86	±0.1672	2.6472
Premenstrual	33.50	±0.1986	3.0736

From Oct. 4 to Dec. 11, 1928, subject C. C. lived on the following diet, weighed to the nearest gram:

Lunch

Eggs	100 Gm
Potatoes	100 Gm.
Crisco	10 Gm.
Butter	10 Gm.
Bread (whole wheat)	200 Gm.
Milk	465 Cc.

Dinner

Vac-Dri Vegetable Mixture	30 Gm.
Dried beef	30 Gm
Canned tomatoes	150 Gm.
Bread (whole wheat)	200 Gm.
Butter	10 Gm.
Loganberry jam (60 per cent dextrose)	100 Gm.
Coffee	200 Cc.

Total ration, 1,200 Calories

During this period, subject C. C. did an almost invariable amount of routine work seven days each week.

The desired results were not obtained, since the diet proved to be slightly deficient in calories. The weight of the subject decreased about 7 per cent (9 pounds [4.1 Kg.]) during this period. The decrease in basal metabolic rate and duration of menstruation are well represented

in chart 1 for C. C., from October 10 to December 12. It is interesting to note that these effects were obtained on a diet so slightly deficient that the deficiency was not detected for about a month.

CONCLUSIONS

From this study it is concluded that:

1. The basal metabolic rate tends to reach its lowest level following menstruation and its highest level preceding menstruation.

2. A deficient diet decreases not only the basal metabolic rate but also the duration of menstruation and the length of the menstrual cycle.

CALCIUM METABOLISM IN ARTHRITIS*

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As the salts of lime form the greatest part of the inorganic portion of all the bones and of the teeth in the body, a study of the calcium metabolism in arthritis with bony changes is of interest. The mineral metabolism of the body is an important part of the general metabolism. Calcium salts are essential to most forms of life, and lime salts are present to a considerable amount in the tissues.

The present experimental study deals largely with the question of the calcium balance in the toxic type of arthritis. Two cases were studied intensively for many weeks. The first case was one of extensive hypertrophic osteo-arthritis in a woman, aged 60, who was more or less bedridden. The other patient was a woman, aged 55, who suffered from generalized atrophic osteo-arthritis. The following classification of arthritis is used.

Rheumatic:	By this term acute rheumatic fever only is meant.
Traumatic:	Simplest form is synovitis such as housemaid's knee.
Hemorrhagic:	Hemarthrosis is really a synovitis with hemorrhage into the joint. This may occur in hemophilia.
Neuropathic:	Charcot's: syringomelia of the spine.
Septic:	Streptococci or staphylococcic infection of the joint introduced from the outside.
Infectious:	From known systemic infections such as typhoid, pneumonia, influenza, tuberculosis, gonorrhea.
Toxic:	(*a*) Hypertrophic osteo-arthritis (*b*) Atrophic osteo-arthritis (*c*) *A* combination of (*a*) and (*b*) This last group includes the so-called rheumatoid arthritis and arthritis deformans. All cases show bony changes.

A great deal of interest is attached to the absorption, excretion and utilization of calcium salts. Lime salts being nearly all insoluble are absorbed with great difficulty from the stomach and intestinal tract and retard the absorption of fluid. They would have a cathartic action were it not for the fact that they are thrown out of solution by the alkaline salts. The greater portion of calcium when given by mouth as medicine undoubtedly leaves the body unabsorbed. When calcium is given intravenously there is an initial elevation of the blood calcium, but it is

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* From the Scripps Metabolic Clinic.

largely excreted. The excess calcium which is stored in some unknown locality in the body is gradually excreted.

In order to study the calcium balance it was necessary to determine the calcium intake and the calcium excretion. Calcium intake was chiefly in the form of food: milk, cheese and milk products, nuts, beets, egg-yolks and molasses contain high amounts of calcium. The calcium intake in the form of ordinary drinking water was negligible, but for

TABLE 1.—*Low Calcium Diet Used in Hypertrophic Osteo-Arthritis, Giving the Amounts of Inorganic Constituents Present as Well as the Total Calories*

Food	Grams	Protein	Fat	Carbohydrate	Calcium	Sodium Chloride	Magnesium
Breakfast							
Grapejuice	100	0	0	16	0.0110	0.0030	0.0090
Cream, 20 per cent	30	1	6	2	0.0258	0.0390	0.0033
Butter, salt-free	20	0	17	0	0.0020	0.0260	0.0006
Puffed rice	15	1	0	12	0.0013	0.0138	0.0049
Egg	50	7	6	0	0.0335	0.0900	0.0056
Bacon	10	3	1	0	0.0011	0.1000	0.0118
White toast	10	1	0	6	0.0027	0.0700	0.0023
Total		13	30	36	0.0784	0.3418	0.0371
Lunch							
Butter, salt-free	10	0	9	0	0.0015	0.0130	0.0002
Salad							
Pineapple, canned	50	1	0	15	0.0090	0.0100	0.0055
Mayonnaise	20	0	17	0	0.0002	0.0028	0.0000
Blackberries	50	1	0	6	0.0085	0.0085	0.0105
White toast	10	1	0	6	0.0027	0.0700	0.0023
Butter, salt-free	20	0	17	0	0.0020	0.0260	0.0006
Egg plant	100	1	0	3	0.0110	0.0205	0.0150
Beef tongue	80	18	6	0	0.0104	0.0880	0.0044
Total		22	49	30	0.0463	0.2288	0.1282
Dinner							
Butter, salt-free	30	0	26	0	0.0045	0.0390	0.0005
Salad							
Asparagus	60	1	0	2	0.0150	0.0096	0.0066
Mayonnaise	20	0	17	0	0.0002	0.0028	0.0000
Peach, canned	80	1	0	24	0.0128	0.0048	0.0080
White toast	10	1	0	6	0.0027	0.0700	0.0023
Tomato	100	1	0	3	0.0110	0.0570	0.0100
Butter, salt-free	10	0	9	0	0.0015	0.0130	0.0002
Baked potato	100	2	0	18	0.0140	0.0650	0.0280
Roast veal	75	19	5	0	0.0105	0.0975	0.0685
Total		25	57	53	0.0722	0.3887	0.1441
Grand total		60	136	119	0.1969	0.9608	0.3094
Calories		1,940					

accurate observations distilled water was given. Distilled water was also used for the making of tea and coffee.

The calcium content of a diet can be varied from 200 to 2,000 mg. of calcium daily with perfect ease, at the same time giving the patient a well balanced, nourishing diet. Sample menus are given in tables 1 and 2.

The calcium metabolism of an arthritic patient can be studied and the diets changed as readily for content of mineral salts as the study of the tolerance of a diabetic patient for foods containing fat, protein and carbohydrate. The foods were accurately weighed, and any food

not eaten by the patient was reweighed in order to have accurate data. Any foods having a variable calcium content were preferably analyzed before being allowed in the diet. No medicine containing calcium was allowed at any time, unless experimentally, and then the calcium content was estimated. The figures of Friedenwald and Ruhräh,[1] of Sherman [2]

TABLE 2.—*High Calcium Diet Used in Atrophic Osteo-Arthritis, Giving the Amounts of Inorganic Constituents Present as Well as the Total Calories*

Food	Grams	Protein	Fat	Carbohydrate	Calcium	Sodium Chloride	Magnesium	Iron
Breakfast								
Milk	200	6	8	10	0.2400	0.3200	0.0240	0.0005
Cream, 40 per cent.	100	3	40	4	0.0860	0.1300	0.0100	0.0004
Butter, salt-free	20	0	17	0	0.0060	0.0060	0.0003	0.0000
Strawberries	150	2	0	11	0.0205	0.0150	0.0285	0.0012
Shredded wheat	30	3	0	23	0.0123	0.0333	0.0480	0.0015
Eggs	100	14	12	0	0.0670	0.1800	0.0110	0.0015
Bacon	20	7	2	0	0.0022	0.2000	0.0236	0.0030
Whole wheat bread	30	3	0	16	0.0150	0.3090	0.0134	0.0005
Total		38	79	64	0.4460	1.1983	0.1888	0.0086
Lunch								
Milk	200	6	8	10	0.2400	0.3200	0.0240	0.0005
Cream, 20 per cent.	50	2	10	3	0.0430	0.0650	0.0050	0.0002
Butter, salt-free	20	0	17	0	0.0060	0.0060	0.0003	0.0000
Salad								
Cottage cheese	50	11	1	2	0.4655	0.1000	0.0185	0.0006
Pineapple, canned	100	1	0	30	0.0180	0.0200	0.0110	0.0005
Lettuce	20	0	0	0	0.0086	0.0250	0.0037	0.0001
Mayonnaise	20	0	17	0	0.0002	0.0416	0.0000	0.0000
Fresh cherries	200	2	0	34	0.0380	0.2060	0.0160	0.0008
Whole wheat bread	20	2	0	10	0.0100	0.0100	0.0236	0.0004
Rhubarb sauce	100	1	0	30	0.0440	0.0000	0.0170	0.0010
Hubbard squash	100	1	0	9	0.0190	0.0500	0.0110	0.0006
Butter, salt-free	10	0	9	0	0.0015	0.0030	0.0000	0.0000
Bacon	20	7	2	0	0.0022	0.2000	0.0236	0.0030
Liver	100	23	4	0	0.0120	0.1400	0.1180	0.0540
Total		56	68	128	0.9050	1.1866	0.2747	0.0617
Dinner								
Buttermilk	200	6	2	10	0.2100	0.3500	0.0240	0.0005
Cream, 20 per cent.	100	3	20	5	0.0860	0.1300	0.0100	0.0004
Butter, salt-free	30	0	26	0	0.0045	0.0090	0.0003	0.0000
Salad								
Dates	30	1	0	21	0.0150	0.0066	0.0230	0.0010
Grapefruit	100	1	0	5	0.0210	0.0050	0.0090	0.0003
Lettuce	20	0	0	0	0.0086	0.0250	0.0037	0.0001
Mayonnaise	10	0	9	0	0.0001	0.0208	0.0000	0.0000
Prunes	100	1	0	20	0.0540	0.0290	0.0550	0.0030
Whole wheat bread	20	2	0	10	0.0100	0.0100	0.0236	0.0004
Spinach	150	2	0	5	0.1005	0.1875	0.0360	0.0027
Parsnip	100	1	0	14	0.0590	0.0510	0.0340	0.0006
Baked potato	100	2	0	18	0.0140	0.0657	0.0280	0.0013
Steak	90	21	14	0	0.0063	0.0990	0.1062	0.0145
Total		40	71	108	0.5890	1.0686	0.3558	0.0248
Grand total		134	218	300	1.9400	3.4485	0.8193	0.0951
Calories	3,698							

and those in Government Bulletin, No. 28 were used for the basis of the mineral content and food values in the diets. An excess of sodium chloride in the diets was avoided to prevent any undue increase in the

1. Friedenwald, J., and Ruhräh, J.: Diet in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, p. 753.

2. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 2, New York, The Macmillan Company, p. 421.

absorption of calcium,[3] and for the same reason diets high in carbohydrate were not given.[4] Excesses of potassium and magnesium in the diet were not allowed, as these salts retard the absorption of calcium.[5]

Calcium excretion was mainly by the bowel in insoluble form. Approximately 90 per cent of the calcium was eliminated by the bowel and 10 per cent by the kidneys. Small amounts of calcium were eliminated by perspiration and exhalation. When phosphates were present in increased amount in the body, more of the calcium was excreted by the bowel as the insoluble calcium phosphate. If the chloride content of the body was high, more of the calcium was excreted in the urine as the soluble calcium chloride.

In order to determine the calcium output it was therefore necessary to make accurate daily twenty-four hour collections of the stools and urine for many weeks. Patients were chosen for this study who were not constipated in order that daily collections of the stools were obtained without the use of cathartics.

METHODS EMPLOYED

The estimation of the calcium in the stool and urine was made by the method of Kramer and Tisdall.[6] In the determination of the calcium content of the stool, each whole stool was saved and evaporated over the water bath, and the air-dried weight of the whole stool was used as the basis for the determination of the calcium. Two grams of powdered stool was used in each case for the actual calcium determination. In the determination of the calcium content of the urine 100 cc. from the twenty-four hour collection was evaporated to dryness over the water bath, and the residue was used as the further basis for the determination.

During the course of this study, a determination of the calcium content of the blood was made in fifty normal cases. The method of Kramer and Tisdall[7] was again used. The older methods used in determination of the calcium in the blood included various types, gravimetric, colorimetric, nephelometric and volumetric, and the values reported varied tremendously. Most of the blood calciums were allowed to be precipitated twenty-four hours before the determination. The specific time of thirty minutes was allowed in all of the present determinations. For an excellent review of the literature on calcium metabolism the reader is referred to an article by Stewart and Percival.[8] The

3. Richards, Godden and Husband: Biochem. J. **18**:651, 1924.
4. Bergeim, O.: J. Biol. Chem. **70**:35, 1926.
5. Bogert, L. J., and McKittrick, E. J.: J. Biol. Chem. **54**:363, 1922.
6. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **48**:1, 1921.
7. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **47**:475, 1921.
8. Stewart, C. P., and Percival, G. H.: Physiol. Rev. **8**:283, 1928.

calcium determinations were all done on the serum calcium which was nonhemolized, and duplicate determinations were made. Hemolysis of the red blood cells invariably resulted in obtaining a lower figure for the serum calcium. In a series of fifty normal persons it was found that the serum calcium ranged from 9 to 10.4 mg. per hundred cubic centimeters of nonhemolized serum. In an analysis of 200 patients the highest serum calcium found was 12.2 mg. per hundred cubic centimeters in a case of hypertrophic osteo-arthritis. Of fourteen patients with hypertrophic osteo-arthritis, ten had serum calciums above 10.5 mg. per hundred cubic centimeters, and in four it fell within the normal limit. Five patients with chronic glomerular nephritis, all in the end-stage but not moribund nor dehydrated, showed low serum calciums ranging from 6.8 to 8.2 mg. per hundred cubic centimeters. One patient with multiple myeloma had a blood calcium of 17 mg. per hundred cubic centimeters of serum, and another patient with carcinoma of the prostate with extensive rarefaction of the pelvic bones with metastases had a blood calcium of 16.5 mg. In the dog, distinctly higher blood calciums were found. In a series of more than 100 determinations on normal dogs, the serum calcium ranged from 10.8 to 12 mg. per hundred cubic centimeters.

EXPERIMENTAL DATA

In table 3 are recorded certain data obtained from the case of hypertrophic osteo-arthritis. In the first column the calcium intake for each day is charted, followed in the second column by the daily calcium excretion in the stool and in the third column by the daily calcium excretion in the urine. The fourth column gives the total calcium excretion for each day. In the last column the daily calcium balance is tabulated.

For the first four weeks this patient was given a general diet, and during the last two weeks the calcium metabolism was followed. During that time there was a retention of 1.178 Gm. of calcium in the system. For the next week a diet not exceeding 200 mg. of calcium daily was given, and it was found that there was a negative calcium balance and 2.575 Gm. of calcium was lost from the system. For the next nine days the same low calcium diet was given, but 20 drops of 10 per cent hydrochloric acid were administered three times a day before meals. The effect of the hydrochloric acid was to increase the percentage of calcium excretion by the urine and to decease slightly the total amount of calcium lost from the system. For the following six days the same dosage of phosphoric acid was given, and although the calcium excretion by the urine was in the same proportion as when hydrochloric acid was used there was decidedly less calcium lost from

TABLE 3.—*The Changes in the Calcium Balance Noted as a Result of Dietetic and Drug Therapy Obtained in a Case of Hypertrophic Osteo-Arthritis*

Date	Calcium Intake, Gm.	Calcium in Stool, Gm.	Calcium in Urine, Gm.	Calcium Output, Gm.	Calcium Balance, Gm.
General Diet					
January 24	0.658	0.764	0.078	0.842	—0.184
25	1.164	0.542	0.074	0.616	+0.548
26	0.921	0.648	0.072	0.720	+0.201
27	0.596	0.642	0.066	0.708	—0.113
28	0.886	0.596	0.078	0.676	+0.210
29	0.599	0.624	0.074	0.698	—0.099
30	0.871	0.594	0.080	0.674	+0.197
31	0.636	0.630	0.062	0.692	—0.246
February 1	0.661	0.764	0.069	0.833	—0.172
2	0.545	0.521	0.066	0.587	—0.042
3	0.564	0.466	0.069	0.535	+0.029
4	0.963	0.449	0.076	0.525	+0.408
5	1.167	0.450	0.074	0.524	+0.643
6	0.609	0.832	0.070	0.902	—0.293
	10.900	8.714	1.008	9.722	+1.178
Low Calcium Diet					
February 7	0.145	0.542	0.052	0.594	—0.449
8	0.184	0.648	0.059	0.707	—0.523
9	0.147	0.541	0.052	0.593	—0.446
10	0.151	0.403	0.051	0.454	—0.303
11	0.187	0.246	0.042	0.288	—0.101
12	0.205	0.344	0.068	0.412	—0.207
13	0.204	0.696	0.055	0.750	—0.546
	1.223	3.419	0.379	3.798	—2.575
Low Calcium Diet with 10 per Cent Hydrochloric Acid, 20 Drops Three Times Daily Before Meals					
February 14	0.194	0.346	0.039	0.385	—0.191
15	0.153	0.300	0.050	0.350	—0.197
16	0.177	0.176	0.047	0.223	—0.046
17	0.144	0.940	0.057	0.997	—0.853
18	0.200	0.427	0.057	0.484	—0.284
19	0.200	0.400	0.063	0.563	—0.353
20	0.181	0.162	0.066	0.228	—0.047
21	0.188	0.332	0.062	0.394	—0.206
22	0.197	0.344	0.034	0.378	—0.181
	1.634	3.517	0.475	3.992	—2.358
Low Calcium Diet with 10 per Cent Phosphoric Acid, 20 Drops Three Times Daily Before Meals					
February 23	0.173	0.342	0.032	0.374	—0.201
24	0.196	0.236	0.020	0.256	—0.060
25	0.152	0.164	0.028	0.192	—0.040
26	0.199	0.216	0.031	0.247	—0.048
27	0.193	0.168	0.021	0.189	+0.004
28	0.190	0.159	0.034	0.193	—0.003
	1.103	1.275	0.176	1.451	—0.348
Low Calcium Diet with Sodium Salicylate, 15 Grains, Three Times Daily Before Meals					
March 1	0.199	0.212	0.038	0.250	—0.051
2	0.198	0.298	0.042	0.340	—0.142
3	0.190	0.322	0.054	0.376	—0.186
4	0.166	0.314	0.058	0.372	—0.206
5	0.181	0.316	0.066	0.382	—0.201
6	0.175	0.420	0.060	0.480	—0.305
7	0.187	0.301	0.052	0.353	—0.166
8	0.193	0.332	0.048	0.380	—0.187
9	0.199	0.241	0.055	0.296	—0.097
10	0.208	0.357	0.050	0.407	—0.199
	1.896	3.113	0.523	3.636	—1.740
Same Diet but with Sodium Bicarbonate, 10 Gm., Three Times Daily Before Meals					
March 11	0.161	0.379	0.046	0.425	—0.264
12	0.195	0.401	0.042	0.443	—0.248
13	0.132	0.412	0.031	0.443	—0.311
14	0.203	0.444	0.038	0.482	—0.279
15	0.200	0.396	0.032	0.428	—0.228
16	0.194	0.493	0.049	0.542	—0.348
	1.085	2.525	0.238	2.763	—1.678

the system. The diet still was the same low calcium diet (200 mg. daily) (table 1). For the next ten days the patient was given 15 grains (0.972 Gm.) of sodium salicylate three times daily in place of the phosphoric acid. This time there was a marked increase in the urine calcium accompanied by an increased total excretion of calcium more comparable to the total calcium excreted during the period in which hydrochloric acid was given. Finally, for six days sodium bicarbonate was administered in 10 Gm. doses three times a day before meals. During this period, the amount of calcium excreted by the urine was markedly decreased although the total calcium excreted was again increased and 1.678 Gm. of calcium was lost from the system.

During the whole period, the blood calcium remained almost constant, being the highest, 11.2 mg. per hundred cubic centimeters, on January 24, and the lowest, 10.8 mg. per hundred cubic centimeters, on March 8. The carbon dioxide combining power of the plasma and the red blood count were normal throughout.

It was noted that the calcium equilibrium was changed from a positive to a negative balance by means of a diet low in calcium. Phosphoric acid greatly retarded the loss of calcium from the system, much more so than hydrochloric acid or sodium salicylate. Sodium salicylate markedly increased the amount of calcium excreted in the urine. Hydrochloric acid and phosphoric acid also increased the percentage of calcium eliminated by the urine but to a less degree. Sodium bicarbonate increased the total amount of calcium lost from the system and markedly decreased the amount of calcium excreted in the urine.

The second case studied was one of atrophic osteo-arthritis (table 4). As the x-ray pictures in this case showed a marked loss of lime salts from the bones of the body, while in the first case an increased density was reported, as nearly as possible a duplicate study of this patient was made for comparative purposes. For the first eleven days the patient was given a general diet, and during this time there was a loss of 4.881 Gm. of calcium from the system. For the following five days a diet low in calcium was employed and there was such a marked loss of calcium noticed that on this account a diet moderately high in calcium and moderately high in calories was next given. On this diet, a negative calcium balance was changed to a positive balance, and in ten days there was a retention of 3.694 Gm. of calcium. For the next two weeks a diet high in calcium was given, and the calcium balance became still more positive (table 4). Up to this time no medication had been given.

Dilute phosphoric acid in doses of 20 drops before meals was given for the following twelve days. During this period, the calcium balance

TABLE 4.—*The Changes in the Calcium Balance Noted as a Result of Dietetic and Drug Therapy Obtained in a Case of Atrophic Osteo-Arthritis*

Date	Calcium Intake, Gm.	Calcium in Stool, Gm.	Calcium in Urine, Gm.	Calcium Output, Gm.	Calcium Balance, Gm.
General Diet; No Medication					
March 22	0.440	0.942	0.086	1.028	—0.588
23	0.684	0.858	0.120	0.978	—0.294
24	0.406	0.902	0.104	1.006	—0.600
25	0.428	0.584	0.119	0.703	—0.275
26	0.475	0.841	0.255	1.096	—0.621
27	0.410	0.788	0.123	0.911	—0.501
28	0.708	0.659	0.111	0.770	—0.062
29	0.673	2.137	0.171	2.308	—1.635
30	0.461	0.232	0.240	0.472	—0.011
31	0.589	0.526	0.264	0.790	—0.201
April 1	0.631	0.464	0.260	0.724	—0.093
	5.905	8.933	1.853	10.786	—4.881
Low Calcium Diet; No Medication					
April 2	0.196	0.502	0.157	0.659	—0.463
3	0.237	0.421	0.198	0.619	—0.382
4	0.184	0.567	0.094	0.661	—0.477
5	0.207	0.353	0.072	0.425	—0.218
6	0.175	0.458	0.128	0.586	—0.411
	0.999	2.301	0.649	2.950	—1.951
General for Calcium but Moderately High Calorie Diet; No Medication					
April 7	0.984	0.179	0.149	0.328	+0.656
8	1.339	0.258	0.176	0.434	+0.905
9	1.350	0.302	0.082	0.384	+0.966
10	0.898	0.987	0.153	1.140	—0.242
11	0.603	0.215	0.084	0.299	+0.304
12	1.305	0.524	0.072	0.596	+0.709
13	0.891	0.720	0.036	0.756	+0.135
14	0.868	0.804	0.046	0.850	+0.018
15	0.825	0.650	0.116	0.766	+0.059
16	0.868	0.560	0.124	0.684	+0.184
	9.931	5.199	1.038	6.237	+3.694
High Calcium Diet; No Medication					
April 17	2.23	0.633	0.052	0.685	+1.545
18	1.60	0.414	0.054	0.468	+1.132
19	2.18	0.550	0.090	0.640	+1.540
20	1.39	0.473	0.045	0.518	+0.872
21	2.13	1.876	0.040	1.916	+0.214
22	2.12	1.094	0.083	1.177	+0.943
23	1.94	0.555	0.083	0.638	+1.302
24	2.09	1.920	0.255	2.175	—0.085
25	2.20	2.056	0.051	2.107	+0.093
26	1.43	2.278	0.138	2.416	—0.986
27	1.29	1.642	0.186	1.828	—0.538
28	1.95	1.408	0.039	1.447	+0.503
29	1.81	1.821	0.073	1.894	—0.084
	24.36	16.720	1.189	17.909	+6.451
High Calcium Diet with 10 per Cent Phosphoric Acid, 20 Drops Three Times Daily Before Meals					
April 30	2.088	1.082	0.059	1.141	+0.947
May 1	1.798	1.123	0.105	1.228	+0.570
2	1.571	0.533	0.102	0.635	+0.936
3	2.483	0.720	0.258	0.978	+1.505
4	1.779	1.011	0.211	1.222	+0.557
5	1.897	0.842	0.108	0.950	+0.947
6	1.724	1.118	0.059	1.177	+0.547
7	1.350	0.833	0.154	0.987	+0.363
8	0.595	0.789	0.210	0.999	—0.404
9	1.168	0.845	0.338	1.183	—0.015
10	1.861	1.080	0.336	1.416	+0.445
11	1.857	0.821	0.067	0.888	+0.969
	20.171	10.797	2.007	12.804	+7.367

TABLE 4.—*The Changes in the Calcium Balance Noted as a Result of Dietetic and Drug Therapy Obtained in a Case of Atrophic Osteo-Arthritis—Continued*

Date	Calcium Intake, Gm.	Calcium in Stool, Gm.	Calcium in Urine, Gm.	Calcium Output, Gm.	Calcium Balance, Gm.
High Calcium Diet with Sodium Bicarbonate, 10 Gm. Three Times Daily Before Meals					
May 12	1.943	1.401	0.200	1.661	+0.282
13	1.864	1.193	0.118	1.311	+0.553
14	1.874	1.016	0.160	1.176	+0.698
15	2.351	1.057	0.276	1.333	+1.018
16	1.914	1.344	0.079	1.423	+0.491
17	0.407	1.754	0.052	1.806	−1.399
18	2.179	1.022	0.087	1.109	+1.070
19	1.285	1.044	0.078	1.122	+0.163
20	1.651	0.644	0.092	0.736	+0.915
	15.468	10.475	1.202	11.667	+3.791
High Calcium Diet with 10 per Cent Hydrochloric Acid, 20 Drops Three Times Daily Before Meals					
May 21	1.135	0.428	0.244	0.672	+0.463
22	1.856	0.545	0.383	0.928	+0.928
23	2.538	1.200	0.398	1.658	+0.880
24	1.508	1.204	0.297	1.501	+0.007
25	1.800	1.800	0.501	2.301	−0.441
26	2.316	1.254	0.480	1.734	+0.582
27	1.518	0.355	0.352	0.707	+0.811
28	2.673	1.434	0.380	1.814	+0.859
29	0.587	1.227	0.220	1.447	−0.860
30	1.909	0.657	0.267	0.924	+0.985
31	1.694	1.039	0.336	1.375	+0.319
June 1	2.090	0.595	0.307	0.902	+1.188
2	2.311	1.770	0.365	2.135	+0.176
	23.995	13.568	4.530	18.098	+5.897
High Calcium Diet with Sodium Salicylate, 15 Grains Three Times Daily Before Meals					
June 3	1.794	0.897	0.220	1.117	+0.677
4	2.226	1.036	0.372	1.408	+0.818
5	1.927	1.242	0.302	1.544	+0.383
6	2.121	0.664	0.376	1.040	+1.081
7	2.500	1.104	0.267	1.371	+1.129
8	0.722	1.211	0.341	1.552	−0.830
9	1.367	0.623	0.426	1.049	+0.318
10	2.102	0.763	0.410	1.173	+0.929
11	2.150	1.140	0.396	1.536	+0.614
12	1.780	1.252	0.415	1.667	+0.113
13	2.532	1.021	0.332	1.353	+1.179
14	1.984	1.418	0.254	1.672	+0.312
15	1.836	1.629	0.444	2.073	−0.237
16	1.305	1.001	0.526	1.527	−0.222
17	2.080	0.762	0.472	1.234	+0.846
	28.426	15.763	5.553	21.316	+7.110

became most markedly positive, and 7.367 Gm. of calcium was retained. For the next nine days, during which time sodium bicarbonate was given in doses of 10 Gm. before meals, the calcium balance was much less positive. There was a marked reduction in the calcium excretion in the urine, the amount falling as low as 10.3 per cent as compared to that of 16 per cent obtained while phosphoric acid was being administered. Dilute hydrochloric acid was then given in doses of 20 drops before meals. During this period of thirteen days, the amount of calcium excreted by the kidneys went to 25 per cent of the total excretion. There was less calcium lost from the system than during the period that sodium bicarbonate was given, but more calcium was excreted than during the use of phosphoric acid. During the final

ten day period, sodium salicylate was given in doses of 15 grains three times daily before meals. The calcium excretion in the urine rose to approximately 26 per cent of the total. This was the highest relative amount to be excreted in the urine in both cases. The calcium balance remained appoximately the same as there was less calcium found in the stools.

During the total period of observation, the serum calcium remained practically constant at 10.8 mg. per hundred cubic centimeters, and the blood counts did not change appreciably. On two occasions, for a period of a week, the nitrogen excreted in the urine exceeded the intake, but when more protein was allowed in the diet nitrogenous equilibrium resulted. The type of diet used in this case is given in table 2.

TABLE 5.—*Tabulation for Comparative Purposes, Showing the Changes in the Calcium Balance Obtained in Hypertrophic and Atrophic Osteo-Arthritis*

Diet	Medication	Calcium in Stool, per Cent of Total	Calcium in Urine, per Cent of Total	Average Daily Calcium Balance, Gm.
Hypertrophic Osteo-Arthritis				
General		89.6	10.4	+0.084
Low calcium		90.1	9.9	—0.368
Low calcium	10 per cent hydrochloric acid, 20 drop three times daily	88.1	11.9	—0.262
Low calcium	10 per cent orthophosphoric acid, 20 drops three times daily	87.9	12.1	—0.058
Low calcium	Sodium salicylate, 15 grains three times daily	85.6	14.4	—0.174
Low calcium	Sodium bicarbonate, 10 Gm. three times daily	91.4	8.6	—0.279
Atrophic Osteo-Arthritis				
General		82.9	17.1	—0.444
Low calcium		78.0	22.0	—0.290
High calorie		83.3	16.7	+0.309
High calcium		93.4	6.6	+0.500
High calcium	10 per cent orthophosphoric acid, 20 drops three times daily	84.0	16.0	+0.614
High calcium	Sodium bicarbonate, 10 Gm. three times daily	89.7	10.3	+0.420
High calcium	10 per cent hydrochloric acid, 20 drops three times daily	75.0	25.0	+0.454
High calcium	Sodium salicylate, 15 grains three times daily	74.0	26.0	+0.474

Table 5 is a summary of tables 3 and 4 and shows the type of diet used, the medication and the average daily percentage of calcium excreted in the stool and in the urine, and also gives the average daily calcium balance.

SUMMARY

1. The daily calcium metabolism in two cases of toxic arthritis was studied for many weeks.

2. A retention of calcium was found in the patient with hypertrophic osteo-arthritis.

3. A loss of calcium or a negative calcium balance existed in the patient with atrophic osteo-arthritis.

4. The calcium balance was altered by dietetic means.

5. The effect on the calcium balance of several medicines commonly used in the treatment for arthritis was observed.

6. Phosphoric acid caused a retention or a better utilization of calcium.

7. All acids used increased the proportionate amount of calcium excreted in the urine.

THE PERIPHERAL SURFACE TEMPERATURE IN ARTHRITIS *

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Interest in the problem of arthritis is increasing. This is owing partly to the fact that insurance of the working classes, especially in Europe, is forcing the problem de novo on the medical conscience, and partly to the internal growth of the topic through the efforts of the relatively small number of persons who have for some years been investigating the disease. This number is now growing, however. A wider outlook on the problem of arthritis is also being developed. The important advance chronicled by the search for and removal of focal infections, not only in arthritis but in many diseases, has often had the incidental effect of directing attention away from those departures in physiology which actually constitute the disease syndrome. This has been less the case in Europe than in this country. It is probably fair to say that the emphasis placed on focal infection in America has achieved a meticulousness of technic which in general exceeds that available elsewhere and has consequently had more signal success. In Europe, the attitude of the profession has been somewhat less crystallized toward the problem, and has therefore included more consideration of the other factors operative to produce rheumatoid disability such as heredity, age, bodily constitution, the climacteric, exposure, intestinal dysfunction and the food intake. In this respect, the European point of view represents a wider range of vision than has been maintained, in general, in this country.

Close students of arthritis realize that after giving infectious factors their fullest value from both the etiologic and the therapeutic standpoint, there is a large and distressing number of sufferers from arthritis who cannot be benefited along this line of attack. Even if it be postulated, for the sake of argument, that all cases of arthritis of every variety are due to infection and that such infection is invariably of a single specific nature, it is obvious that one is a long way from being able to apply, in an adequately successful manner, therapy based on this concept. As a matter of fact, however, it is common knowledge

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that not only is there a great difference of opinion among students of the disease as to the importance of the rôle played by infection in the several forms of arthritis, especially hypertrophic arthritis, but, even when infectious processes are acceptedly concerned, it is again common knowledge that many varieties of organisms may be operative. These varieties include not only the many strains of streptococcus (viridans, hemolyticus, nonhemolyticus and intermediary forms), but also such organisms as the gonococcus, staphylococcus, colon bacillus, pneumococcus and others.

In view of the foregoing considerations, it can hardly be doubted that there is need for information bearing on the disturbances in physiology, whatever their etiology, productive of the phenomena and symptoms of the disease. Even in tuberculosis and syphilis, concerning which knowledge of the etiologic factors is relatively clearcut, study of the deviations of physiology accompanying the disease cannot be ignored; and, in point of fact, the treatment for tuberculosis rests today chiefly on empiric and physiologic, rather than purely bacteriologic, considerations.

It is apparently necessary to point out, in some quarters, the fact that study of the physiologic background of arthritis carries no implication of any lesser importance to be attached to such infectious factors as are known to be operative. When these are the exciting agents, the influence of bacteria in the production of arthritis is in no way comparable to the gross depredations of the tubercle bacillus and pus-forming organisms in inducing, for example, liquefaction necrosis. The influence of bacteria in arthritis is achieved, in general, by a more subtle mechanism. Study of this mechanism would probably lead to better, if not complete, understanding of the problem of arthritis and of some other conditions as well. To jump from interest in some of the etiologic factors of arthritis to consideration of only the clinical end-phenomena of the disease is largely to ignore study of the essential disease itself. It is fortunate that the door is now more widely opened for entrance on this phase of study of the problem.

The observations to be recorded have been carried out from the general standpoint just outlined. Within the last eight years we [1] have adduced increasing evidence pointing to the fact that there is in the arthritic syndrome a tendency toward a disturbance of peripheral blood flow which constitutes part of, if not part of the cause of, the objective phenomena of the disease. This evidence has been based somewhat on direct observations of the capillary beds,[2] to be reported elsewhere in

1. Pemberton, Ralph; Hendrix, B. M., and Crouter, C. Y.: J. Metab. Research **2**:301, 1922.

2. Pemberton, Ralph: Arthritis, J. Michigan M. Soc. **26**:599, 1927.

detail, and somewhat on observations of the red cell count in blood obtained from peripheral regions.[3] Other considerations, which cannot be detailed here,[4] strengthen the belief that the peripheral circulation is concerned in the phenomena of arthritis, and it becomes important accordingly to obtain, if possible, further corroboratory data. If there is in arthritis, as has been advanced by us, a tendency toward a sluggish peripheral blood flow and consequent "anemia" or "anoxemia" of the tissues, some expression of this should be found in terms of the local temperature of the part. According to Lewis,[5] there are three methods available for the study of cutaneous circulation: direct microscopic observation, study of the skin color and its changes and study of the skin temperature and its response to various influences. Local temperature is presumably a function of heat production, heat loss and blood flow. In the absence of evidence suggesting disturbance of heat production, and under apparently comparable conditions of heat loss as regards normal and arthritic subjects, changes of temperature at the periphery of arthritic patients can be referred with considerable confidence to changes in the amount or rate of blood flow in the part concerned. It is true that about one fifth of the arthritic patients studied chiefly in the army, and of the atrophic type, showed a lower basal metabolic rate.[5a] It has also been shown, however, by direct calorimetry,[6] that there is no abnormal respiratory metabolism following the ingestion of large test meals of carbohydrate and protein, and the lowered basal metabolic rate encountered in one fifth of arthritic patients is probably to be explained along more mechanical lines. It appears, indeed, to be a reflection of the disturbance of blood supply to many tissues, especially the muscles.[6a] Furthermore, coincident observations already reported in a preliminary way,[2] based on direct inspection of the capillaries, add strong evidence that the surface temperature under the conditions of study is referable chiefly or wholly to the local blood flow.

It has been noted that subjects with arthritis often complain of cold hands and feet and that the nails and finger tips may appear cyanotic or somewhat blanched. In the series of 700 civilians studied

3. Peirce, E. G., and Pemberton, Ralph: The Red Cell Count in Arthritis, Arch. Int. Med. **39**:421 (March) 1927. Crouter, C. Y., and Cajori, F. A.: The Red Cell Count in Arthritis: Second Paper, Arch. Int. Med. **39**:429 (March) 1927.

4. Pemberton, Ralph: Arthritis and Rheumatoid Conditions: Their Nature and Treatment, Philadelphia, Lea & Febiger, 1929.

5. Lewis, T.: The Blood Vessels of the Human Skin, and Their Response, London, Shaw & Sons, 1927, p. 7.

5a. Pemberton (footnote 4, p. 75). Swaim, L. T., and Spear, L. M.: Boston M. & S. J. **197**:350, 1907.

6. Cecil, R. L.; Barr, D. P., and DuBois, E. F.: Clinical Calorimetry: XXXI. Observations on the Metabolism of Arthritis, Arch. Int. Med. **29**:583 (May) 1922.

6a. Pemberton (footnote 4, p. 101).

by E. G. Peirce and one of us (R. P.[6b]), paresthesias of various kinds, suggestive of circulatory disturbance, were encountered with surprising frequency. It became important, therefore, to determine whether or not clinical impressions such as these could be substantiated by more nearly precise methods.

Studies were therefore undertaken on the surface temperature of arthritic subjects at the periphery (fingers, hands and forearms), the method described by Benedict being used; namely, the difference of electric potential developed in a thermocouple, on application to the part, and recorded by a galvanometer. Benedict and Parmenter [7] noted that exposure to severe cold, with or without strenuous exercise, resulted in a lowering of the skin temperature, chiefly of the extremities. Talbot and his associates [8] used this method in determinations of the surface temperatures of children, and Mudd and his collaborators [9] observed a drop in the temperature of the nasal mucosal surface after chilling of the body surface.

It was further partly the object of the present studies to obtain evidence explanatory of the response of the arthritic subject to environmental changes due to the weather. It is well recognized that sufferers from arthritis experience exacerbations more or less coincident with such changes.

Human beings live at the bottom of an ocean of air in which movement, pressure, humidity, temperature and other factors are constantly varying. The influence of climate on persons and even on races is recognized in a wide sense of the word but there would be advantage in attaching precise figures to many current impressions regarding the weather and thus modifying or extending knowledge in this field, especially in relation to disease.

In a series of observations begun during the World War and conducted over several years among arthritic soldiers and civilians,[9a] no fixed relationship was observed between exacerbations in arthritic processes and abrupt changes in temperature, humidity or barometric pressure. It was noted, however, that more or less contemporaneously with exacerbations there was a tendency for the barometer to fall and for the humidity to rise. Since the publication of these results, Rentschler, Vanzant and Rowntree [10] reported "a positive relationship for

6b. Pemberton (footnote 4, p. 45).

7. Benedict, F. G., and Parmenter, H. S.: Am. J. Physiol. **87**:633, 1929.

8. Talbot, F. B.; Dalrymple, A. J., and Hendry, M. E.: Skin and Temperatures in Normal Children, Am. J. Dis. Child **30**:483 (Oct.) 1925.

9. Mudd, S.; Goldman, A., and Grant, S. B.: J. Exper. Med. **34**:11, 1921.

9a. Pemberton (footnote 4, p. 328).

10. Rentschler, E. B.; Vanzant, F. R., and Rowntree, L. G.: Arthritic Pain in Relation to Changes in Weather, J. A. M. A. **92**:1995 (June 15) 1929.

72 per cent of the time between the curve of pain and that of barometric pressure," viz., as the barometric pressure fell, the pain increased and as the barometric pressure rose, the pain decreased in a group of 367 patients. It was decided, therefore, to include in the present observations a study of the response of the arthritic patient to changes in the environment, cold being used as one of the factors concerned in meteorologic changes at large.

METHOD

The apparatus employed was that described by Bazett and McGlone[11] for the determination of surface temperatures, constantan wire and iron wire being used as thermo-elements. The apparatus was calibrated each day. Before the temperature of a given point was taken, the surface thermocouple was warmed by being placed in contact with a nearby point. The points chosen for the determination of the surface temperature were: the palm of the hand between the middle and fourth fingers; the back of the hand at (1) the base of the nail of the middle finger; (2) the midphalangeal joint of the middle finger; (3) the knuckle of the middle finger, and (4) the wrist. When the subject entered the laboratory, he was placed in the room where the study was to be carried out and was allowed to remain until comfortably warm, by which time he or she had presumably approached an equilibrium. This usually required half an hour, or slightly longer. The sleeve of the arm to be studied had meanwhile been rolled to the elbow, all constriction being avoided. The skin temperatures of the aforementioned points were taken every two minutes until the temperature of each point was approximately constant. The attempt was made to obtain readings indicative of a relative constancy of temperature of the hand as a whole in relation to the surrounding medium. Constancy of temperature of each point was not always possible, for the temperature of any given point changes normally. Occasionally, the difference between the successive final readings at any given point was greater than 1 C. It is to be noted, however, that Talbot and his associates[8] found comparable variations in the skin temperature of a group of children covered by a double layer of blankets.

After the foregoing preparation, the subject was then covered with a coat, blankets and a hat. The hand and arm which were being used for study were exposed to the air and the subject was placed in a cold storage room for ten minutes. At the end of that time he was taken out of the cold room, unwrapped and brought back into the aforementioned warm room, as quickly as possible. Skin temperatures were taken at the following intervals: one, three, five, seven, ten, thirteen, sixteen, twenty and twenty-five minutes or two, four, six, eight, ten, thirteen, sixteen, twenty and twenty-five minutes, with occasional exceptions. Few of the experiments were continued beyond the twenty-five minute interval. Some cases were followed in the ward, where the pulse, respiration and systemic temperature could be observed over long periods. These cases showed no deviations from the normal to account for the experimental results obtained. The experiments have been divided into the two following groups:

GROUP 1.—This group consisted of sixteen arthritic and eleven normal subjects. The room in which the subjects were studied contained a door, a ventilator and one window, and the subjects were so placed in this room that drafts were avoided as much as possible. The temperature of the room ranged between 26

11. Bazett, H. C., and McGlone, B.: J. Lab. & Clin. Med. **12**:913 (June) 1927.

and 26.8 C. (78.8 and 80.2 F.). It usually changed not more than 0.8 C. during any observation. The temperature of the cold room, which was controlled by a thermostat, averaged 7.2 C. (45 F.) plus or minus 1 C. One normal subject was studied on the same day as that on which one or more arthritic subjects were studied, the conditions being kept as similar as possible. (There was one exception to this statement: Two arthritic subjects were studied on one day and their normal control was run through on the following day.) The arthritic and the normal control subjects were equally well wrapped in the cold room.

Group 2.—Group 2 included twenty-six arthritic and ten normal subjects. In the studies in group 2, one experiment, on a normal subject, was carried out in a main laboratory room, and six experiments, one on an arthritic subject and five on normal subjects, were carried out in another of the laboratory rooms. These studies were carried out before the importance of drafts was fully appreciated, and each of these rooms was drafty. To avoid this error the subsequent twenty-four subjects from group 2, including twenty-two arthritic and two normal subjects, were studied in the dark room, the circuitous entrance of which effectively cut off all drafts. This room, however, had the disadvantage of becoming humid and warm before the end of the experiment. Experience finally showed that the experiments could be best carried out in the room described under group 1. Three arthritic and two normal subjects of group 2 were studied in here. Except for the last five experiments the attempt was not made to standardize the room temperature, which averaged from 25.5 to 26.1 C. (77.9 to 79 F.). In group 2, a normal control was not run through on the same day as was an arthritic subject, nor were the normal subjects as warmly wrapped in the cold room as the arthritic subjects. The cold room temperature, which was controlled by a thermostat, averaged 6.7 C. (44 F.) plus or minus 1.5 C. In one experiment, the subject was placed outdoors for ten minutes instead of in the cold room, the outdoor temperature being 9.4 C. (49 F.).

RESULTS

Studies of the surface temperature at the base of the nail of the middle finger gave the following results:

In Group 1.—(*a*) The initial temperature of 75 per cent of the arthritic subjects was lower than that of the average normal subject.

The initial temperature of 44 per cent of the arthritic subjects was lower than that of the lowest normal subject, which was 32.1 C.

The average initial temperature of the arthritic subjects was 31.2 C. The average initial temperature of the normal subjects was 33.7 C.

(*b*) After ten minutes in the cold room, 100 per cent of the arthritic subjects showed a lesser drop in temperature than did the average normal subject.

After ten minutes in the cold room, 81 per cent of the arthritic subjects showed a lesser drop in temperature than did any normal subject.

The average drop in temperature was 6.6 C. for the arthritic and 10.7 C. for the normal subjects.

(*c*) Fifty-six per cent of the arthritic subjects returned to the precold room level before the end of the experiment, as compared with 36 per cent of the normal subjects.

The average time of return of skin temperature to the previous level, within 0.1 C., was sixteen for the arthritic and nineteen minutes for the normal subjects.

Calculated on the basis of the rate of return for normal subjects, the arthritic subjects should have returned to the precold room level in twelve instead of sixteen minutes.

The rate of return is only approximated, because graphs show that it is not a straight line function.

In Group 2.—(*a*) The initial temperature of 50 per cent of the arthritic subjects was lower than that of the average normal subject.

The initial temperature of 19 per cent of the arthritic subjects was lower than that of the lowest normal subject, which was 30.2 C.

The average initial temperature of the arthritic subjects was 31.9 C.; that of the normal subjects, 32.7 C.

(*b*) After ten minutes in the cold room, 69 per cent of the arthritic subjects showed a lesser drop in temperature than the average normal subject.

After ten minutes in the cold room, 31 per cent of the arthritic subjects showed a lesser drop in temperature than did any normal subject.

The average drop in temperature was 6.1 C. for the arthritic and 8.3 C. for the normal subjects.

(*c*) Sixty-five per cent of the arthritic subjects returned to the precold room level before the end of the experiment, as compared with 67 per cent of the normal subjects.

The average time of return was twelve for the arthritic and fifteen minutes for the normal subjects.

Calculated on the basis of the rate of return for normal subjects, the arthritic subject should have returned to the initial temperature in eleven instead of twelve minutes.

The observations in group 2, the less accurately controlled group, are in consonance with those in group 1, although the departures from normal are not so great.

Studies of the skin temperature of the midphalangeal joint, of the knuckle, and of the wrist for both groups showed:

(*a*) The difference between the initial temperature of the arthritic and normal subjects was less marked at these points.

(*b*) The drop in temperature of the arthritic and the normal subjects after ten minutes' exposure in the cold room, was also less marked at these points.

(*c*) The difference between the drop in temperature of the arthritic and of the normal subjects, after ten minutes' exposure in the cold room, was less marked at these sites.

(*d*) As the hand and wrist were ascended, the initial temperature of the arthritic approached that of the normal subject, and the drop in temperature of the arthritic subject, aften ten minutes' exposure in the cold room, approached that of the normal subject.

The emphasis placed on the two types of arthritis, namely, atrophic and hypertrophic, which are receiving increasing recognition, makes it desirable to determine the degree to which, if at all, these observations varied in the two types mentioned.

Most of the cases in the present study were of the atrophic variety. In view of the relatively small number of hypertrophic cases in this series, all cases in group 1 and group 2 which could be differentiated into types are considered together.

Atrophic Arthritic Subjects.—Twenty-eight observations were made on twenty-four subjects.

(*a*) The initial temperature of 54 per cent of the atrophic arthritic subjects was lower than that of the average normal subject.

The initial temperature of 25 per cent of atrophic arthritic subjects was lower than that of the lowest normal subject, which was 30.2 C.

The average initial temperature of the atrophic arthritic subjects was 31.7 C. The average initial temperature of the normal subjects was 33.3 C.

(*b*) After ten minutes' exposure in the cold room, 82 per cent of the atrophic arthritic subjects showed a lesser drop in temperature than did the average normal subject.

After ten minutes in the cold room, 21 per cent of the atrophic arthritic subjects showed a lesser drop in temperature than any normal subject.

The average drop in temperature was 6.6 C. for the atrophic arthritic and 9.6 C. for the normal subjects.

(*c*) Sixty-four per cent of the atrophic arthritic subjects returned to the precold room level before the end of the experiment, as compared with 50 per cent of the normal subjects.

The average time of return was fifteen for the atrophic arthritic and sixteen minutes for the normal subjects.

Calculated on the basis of the rate of return for normal subjects, the atrophic arthritic subject should have returned to the initial temperature in eleven instead of fifteen minutes.

Hypertrophic Arthritic Subjects.—Nine observations were made on seven cases.

(*a*) The initial temperature of 78 per cent of the hypertrophic arthritic subjects was lower than that of the average normal subject.

The initial temperature of 22 per cent of the hypertrophic arthritic subjects was lower than that of the lowest normal subject, which was 30.2 C.

The average initial temperature of the hypertrophic arthritic subjects was 31.6 C.; that of the normal subjects was 33.3 C.

(*b*) After ten minutes in the cold room, 100 per cent of the hypertrophic arthritic subjects showed a lesser drop in temperature than did the average normal subject.

After ten minutes in the cold room, 44 per cent of the hypertrophic arthritic subjects showed less of a drop of temperature than did any normal subject.

The average drop in temperature was 4.8 C. for the hypertrophic arthritic and 9.6 C. for the normal subjects.

(*c*) Sixty-seven per cent of the hypertrophic arthritic subjects returned to the precold room level before the end of the experiment, as compared with 50 per cent of the normal subjects.

The average time of return was nine for the hypertrophic arthritic and sixteen minutes for the normal subjects.

Calculated on the basis of the rate of return for normal subjects, the hypertrophic arthritic subject should have returned to the initial temperature in eight instead of 9 minutes.

Indefinite Arthritic Subjects.—Five observations on three indefinite cases of arthritis showed closely comparable changes of the same order as were observed in arthritic subjects as a whole.

Contrary to what might have been expected, since atrophic arthritis is regarded as the more acute condition, these observations appear to indicate that the hypertrophic type shows as great departures from normal as does the atrophic type.

The skin temperature of finger joints, the seat of a frankly inflammatory process, is higher than the skin temperature of the corresponding noninflamed joint of another finger. For example, the initial temperature of an acutely involved joint, in the case of Mrs. Lws., showing atrophic arthritis, was 0.4 C. higher than that of the uninvolved joint; the temperature drop of the involved joint was 3.2 C. less than that of the uninvolved, and the return of the involved joint parallel that of the uninvolved finger of the arthritic subject.

It is to be noted that the lesser drop of the arthritic subjects as compared with that of the normal subjects is referable not alone to having started at a lower level. This is well illustrated by the construction of average curves for the normal and the arthritic subjects

(chart). Such curves show that, although the arthritic subject starts about 2 C. lower, he reaches a low point 1.5 C. higher than the low point of the normal subject.

TABLE 1.—*Study of Temperature of Base of Finger-Nail*

Subjects	Number of Observations	Average Initial Temperature, Centigrade	Per Cent of Arthritic Subjects Below Average Normal Subject	Per Cent of Arthritic Subjects Below Lowest Normal Subject	Average Temperature Drop, Centigrade	Per Cent of Arthritic Subjects with Less Drop Than Average Normal Subject	Per Cent of Arthritic Subjects with Less Drop Than Any Normal Subject	Per Cent of Subjects Showing Return to Initial Temperature	Average Time of Return, Minutes	Rate of Return in Degrees per Min.
Group 1										
Arthritic.....	16	31.2	75	44	6.6	100	81	56	16	0.41
Normal.....	11	33.7			10.7			36	19	0.56
Group 2										
Arthritic.....	26	31.9	50	19	6.1	69	31	65	12	0.51
Normal.....	10	32.7			8.3			67*	15	0.55
Whole Group										
Atrophic arthritic.....	28	31.7	54	25	6.6	82	21	64	15	0.44
Hypertrophic arthritic.....	9	31.6	78	22	4.8	100	44	67	9	0.53
Indefinite arthritic.....	5	31.1	80	20	7.2	100	20	40	13	0.55
Arthritic.....	42	31.6	62	24	6.3	88	20	62	13	0.48
Normal.....	21	33.3			9.6			50†	16	0.60

* Base on nine cases.
† Based on twenty cases.

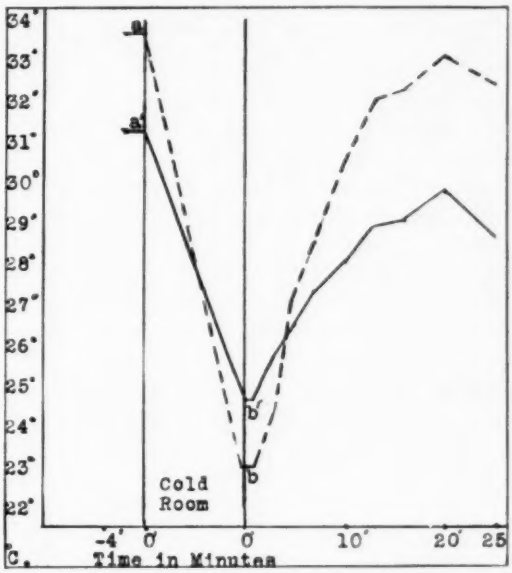
TABLE 2.—*Other Points of the Investigation*

	Midphalangeal Joint			Knuckle			Wrist			Palm		
Subjects	No. of Observations	Average Initial Temperature, Centigrade	Average Temperature Drop, Centigrade	No. of Observations	Average Initial Temperature, Centigrade	Average Temperature Drop, Centigrade	No. of Observations	Average Initial Temperature, Centigrade	Average Temperature Drop, Centigrade	No. of Observations	Average Initial Temperature, Centigrade	Average Temperature Drop, Centigrade
Group 1												
Arthritic	16	31.5	5.2	16	31.5	3.8	16	31.9	3.4	16	32.2	3.7
Normal..	11	33.3	7.9	11	32.8	5.1	11	32.9	4.8	11	33.6	5.2
Group 2												
Arthritic	18	32.5	4.6	18	32.6	3.6	20	32.7	3.2	17	32.9	3.3
Normal..	4	33.2	6.7	4	32.7	5.1	4	32.7	4.4	4	33.5	4.2
Whole Group												
Arthritic	34	32.1	4.9	34	32.0	3.7	36	32.4	3.3	33	32.5	3.5
Normal..	15	33.3	7.6	15	32.8	5.1	15	32.9	4.7	15	33.5	4.9

The fact that the arthritic subject has colder hands than the normal subject, under comparable conditions, was noticed while another group of experiments was being carried out. While preparing the subject for direct capillary observations, it was found that it was more difficult to warm an arthritic subject to the minimum of 32 C. at the base of

the nail, as determined by the thermocouple, and to keep him warm, than was the case with normal subjects. In the winter especially it was frequently necessary to apply a hot water bottle to the hand to bring the temperature of the part to this level. In several cases the arthritic hand, warmed to 32 C., would not stay warm at room temperature long enough for a capillary observation to be made.

Corroboration of the explanation given at the outset for the cold hands of the arthritic subject was obtained by Dr. E. G. Peirce while the capillaries at the bases of the nail were being directly observed. The



The initial surface temperatures at the periphery of normal and arthritic patients and the response to exposure to cold. The broken line represents the normal temperature curve; the solid line, the arthritic temperature curve; *a*, normal initial temperature; *a'*, arthritic initial temperature; *b*, normal temperature after ten minutes' exposure; *b'*, arthritic temperature after ten minutes' exposure.

capillary field [2] of the average arthritic subject contained less blood and was lighter in color than that of the average normal field. This may have been due to the fact that there were fewer capillaries open or to a difference in the size of the capillaries. Under approximately the same conditions of temperature, the blood flow in the capillary field of the average arthritic subject was not so rapid as that in a normal field; it was not so steady, and there were more breaks in the column of blood as it flowed through the capillaries. This arthritic capillary picture was made to

approach the normal by raising the skin temperature at the base of the nail several degrees Centigrade. A detailed report of this work is now in progress.

In keeping with these thermometric observations on forty-two arthritic and twenty-one normal subjects is the observation of Rowntree and Adson [12] on a patient with severe arthritis in whom the operations of bilateral lumbar and cervicothoracic ganglionectomy were followed by an apparent change of color and rise of temperature both in the upper and the lower limbs, which had previously been cold and clammy.

SUMMARY

The observations recorded reveal that, under adequately controlled conditions of study, 75 per cent of arthritic subjects maintain at the periphery, (the base of the nail), a temperature lower than that of normal persons under comparable circumstances. They also show that under conditions of exposure to cold, the temperature of the arthritic subject at the periphery drops less than does that of normal subjects, partly, but not wholly, because of starting at a lower level. The return of the peripheral temperature of the arthritic subject to the precold room level appears to be relatively slower than that of normal subjects. It is difficult to explain these differences between arthritic and normal subjects on a basis other than that of diminution in, or at least disturbance of, the capillary blood flow.

These observations, further, throw light on the mechanism operative in the exacerbations experienced by arthritic subjects during fluctuations in the weather. They imply that the capillary bed, and presumably its control by the vasomotor system, is less labile in respect to adaptations demanded of it by changes in the environment. Inadequacy of response of this nature doubtless expresses itself in terms of further disturbances in the physiology of the part concerned. In the already handicapped tissues of the arthritic subject, this may mean added dysfunction and pain.

Finally, these observations lend further support to the evidence already advanced that an important part of the phenomena of arthritis and the rheumatoid syndrome is referable to disturbances in the peripheral blood flow.

12. Rowntree, L. G., and Adson, A. W.: Polyarthritis: Further Studies on the Effects of Sympathetic Ganglionectomy and Ramisectomy, J. A. M. A. **93**:179 (July 20) 1929.

Book Reviews

A Textbook of Medicine. By Various Authors. Edited by J. J. Conybeare, M.C., M.D. (Oxon.), F.R.C.P. Pp. 947. New York: William Wood & Company, 1929

The contributors, in addition to J. J. Conybeare, are: W. H. Craib, Goeffrey B. Dowling, E. H. R. Harries, Arthur Maitland-Jones, Vernon E. Lloyd, Hugh Maclean, Goeffrey Marshall, Trevor Owen and F. M. R. Walshe. This list of names gives assurance of itself that the book will be a valuable one.

The book contains a compact, concise, clearcut description of every disease commonly grouped under the heading of general medicine. It has in addition sections devoted to neurology and dermatology, including all but the rare conditions occurring in these fields. So it is not only an ideal volume for teaching purposes, but a convenient reference for physicians in any specialty. The intern or young general practitioner would find it particularly useful.

It is a readable work from the point of view of style. One even finds an occasional stroke of humor—a thing appearing all too rarely in medical literature — such as the statement that prohibition in the United States has brought to light the toxic properties of methyl alcohol, or the description of the gambler with gout who made chalk marks on the table with the tophi on his kunckles.

One or two features may detract from the usefulness of the book in this country. Most of the medications are those of the British Pharmacopoea, and while the American equivalent is usually apparent, the change might be somewhat confusing to students.

The discussion of thyrotoxicosis is open to criticism in the light of experience with that disease in the Middle West. Conybeare makes a sharp distinction between the Grave hyperplastic type and the toxic-adenomatous form, and adds that iodine is of no avail in the treatment for the latter. The reader is given no warning that he will meet with many patients having some of the characteristics of both groups. The author says that operation as a rule should not be considered before six months of medical treatment; roentgen treatment, he leads one to believe, should be abandoned. But of course this disease is more common and severe in this country than in England; so the treatment may vary in the two localities.

The rest of the book is sound in every respect. The treatment for syphilis is systematized and detailed in a thorough fashion. The section on diabetes is particularly admirable. It is the equivalent of a handbook on the subject, with diet tables, sample diets and a regimen that uses the best parts of the several schools of treatment without the extremes of any.

The treatment for peptic ulcer does not resemble that of Sippy or Mills, and the drugs are not those in common use in America, but no doubt they accomplish the same results.

The subject of heart disease is well presented. The principles of the electrocardiograph are clearly stated and described in such a way as to be of great assistance to the beginner.

The editor has eminently succeeded in his attempt, as stated in the Preface, "to provide within as small a compass as possible the essentials of medicine, without, however, producing anything in the nature of a synopsis."

Lehrbuch des Stoffwechsels und der Stoffwechselkrankheiten. By Dr. Med. et Phil. S. J. Thannhauser. Price, 56.80 marks. Munich: J. F. Bergmann, 1929.

Thannhauser's book presents a discussion of diseases in which biochemical processes are prominent, by a clinician trained and experienced in biochemistry,

who has himself been an industrious and successful investigator in the field of metabolic disorders. The result is an unusually successful balancing of the clinical and the laboratory points of view, so that each chapter is equally full of interest and suggestion for both the clinician and the laboratory worker. It is based on a series of lectures by the author, who is director of the medical clinic in Düsseldorf, and therefore possesses the advantage of readability usual in published lectures. Such a work cannot exhibit the complete familiarity with all fields expected in books compiled by several specialists, but it does possess the advantage of presenting a balancing and analysis of the specialists' contributions by a qualified physician competently utilizing in the clinic the most recent contributions of the biochemical laboratory. The result is a most useful volume that can be cordially recommended to every progressive physician and biochemist. Excellent selection has been made from the vast literature available, and the author is familiar with more of the world's literature than is always the case with his compatriots. Diabetes receives the most extended discussion, occupying 215 of the 715 pages of text, and it is a well balanced presentation. Purine metabolism and gout are particularly well discussed, the author adhering to the view that there are two sorts of gout, one depending on a selective primary deficiency of the capacity of the kidney to eliminate uric acid, this being unaccompanied by observable anatomic alterations or other defects of the kidney; the other is merely a stage of progressive chronic nephritis in which the retention of uric acid is only a part of the general functional deficiency. Fat metabolism, with its abnormal manifestations of obesity and emaciation, is well covered. Protein metabolism is presented in conventional manner, and the pigmentary metabolism is thoroughly reviewed. There are also sections on total metabolism, and on mineral and water metabolism, including a discussion on neutrality regulation which will probably impress American readers as perhaps less adequate than some of the other presentations. All in all, this "Lehrbuch" offers an excellent middle-power view of the field of metabolic diseases with good perspective and little distortion.

UEBER ORGANHORMONE UND ORGANTHERAPIE. By GEH.-RAT PROF. DR. AUGUST BIER, DR. W. FEHLOW, DR. A. GEHRKE, DR. U. LUETKENS and PRIVAT-DOZENT DR. A. ZIMMER. Price, 4.50 marks. Pp. 91. Munich: J. F. Lehmanns, 1929.

This is not a monograph on hormone therapy, but contains four brief reports on some of the nonsurgical therapies followed in the surgical clinic of Dr. Bier. The first paper is a general discussion, with an account of the experience with intravenous injections of foreign blood by Dr. Bier. An item of great historical interest is referred to, namely, that the ancient Arab and Persian physicians treated patients with severe anemias (we are not told how successfully) by feeding them with liver. If this is correct, the recent liver therapy of anemia is a rediscovery. Dr. Luetkens and Dr. Gehrke report on treatment for diseases of the liver and gallbladder with crude extracts of gallbladders and liver ("Choloton schwach," and "Choloton stark"). Dr. Gehrke states that for many years he has treated patients with tabes, progressive paralysis, multiple sclerosis, etc., by feeding them animal brain substance ("Promonta"). Finally, there is a short account by Dr. Zimmer and Dr. Fehlow on the treatment of patients with toxic goiter by the intravenous injection of foreign blood. They claim that therapy (essentially foreign protein) increases appetite, reduces nervousness and insomnia and increases body weight, by "its deep influence on restoring the harmony of function" (p. 88).

Apart from the distinct foreign protein therapy, a field in which experimentation is still warranted, if one takes steps to control the usual "post hoc" errors, this twentieth century excursion of surgeons into internal medicine reveals little or no advance on the "tiger bone therapy" of the ancients.